

FAMILY MATTERS:

**Relationship dynamics among couples affected by HIV during pregnancy,
and neurodevelopment of HIV-exposed uninfected infants in sub-Saharan Africa**

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A dissertation
submitted in partial fulfillment
of the requirements for the degree of

Doctor of Philosophy

University of Washington

2023

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Program Authorized to Offer Degree:

Public Health – Epidemiology

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Abstract

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Relationship dynamics among couples affected by HIV during pregnancy,
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Chair of the Supervisory Committee:
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Introduction: Caregiver wellbeing is closely linked to child health and neurodevelopmental outcomes. Families affected by HIV in sub-Saharan Africa (SSA) may face increased risk of poverty, parental relationship dissolution, and poorer child neurodevelopment, but these associations are poorly understood. Pregnant women living with HIV (PWLHIV) in sub-Saharan Africa (SSA) are especially vulnerable to adverse consequences of disclosure of their HIV serostatus, including separation, financial hardship, and poor mental and physical health outcomes. The integration of quantitative and qualitative research methods is urgently needed to better understand the predictors and consequences of separation among couples affected by HIV. Perinatal HIV exposure can increase risk of neurodevelopmental delay in children, irrespective of child HIV acquisition. Thanks to remarkable strides in prevention of mother-to-child transmission (PMTCT), there are now nearly 16 million children who are HIV-exposed uninfected (CHEU), with an additional one million CHEU born every year in SSA. It is crucial to identify caregiver-related factors associated with child neurodevelopment to ensure CHEU thrive in a manner comparable to their HIV-unexposed peers.

Methods: This dissertation aimed (**Chapter I**) to identify factors associated with relationship dissolution between Ugandan PWLHIV and their male partners among couples enrolled in a randomized clinical trial and recommend strategies to increase male partner testing and knowledge of HIV serostatus, employing mixed methods using a convergent parallel design, (**Chapter II**) to compare one-year neurodevelopment between Kenyan children with and without perinatal HIV exposure in a prospective longitudinal cohort, and identify caregiver factors associated with poor child neurodevelopment using multivariate linear mixed effects models, and (**Chapter III**) to synthesize latest literature in a commentary about the biologic and social mechanisms through which maternal HIV could impact child neurodevelopment, and to suggest research and advocacy directions to fill knowledge gaps for CHEU.

Results: (**Chapter I**) Separation during pregnancy and postpartum was frequent (23%) among the 500 pregnant Ugandan women living with HIV, and was associated with being in unmarried, non-cohabitating, shorter relationship duration (<1 year), polygamous relationships, as well as HIV non-disclosure and experience of verbal abuse. Participants discussed how HIV serodifferent status, financial burdens, and strong gender expectations led to relationship conflict. Separation was discussed as both a negative and positive outcome depending on couples' circumstances, in terms of mental health, treatment continuation, financial security, and experience with IPV. (**Chapter II**) At one-year evaluation among Kenyan infants, CHUU (N=715) and CHEU (N=416) had comparable neurodevelopment scores across all tested domains. Among all children, after adjusting for confounders selected *a priori* and clustering by site, lower child neurodevelopment scores were significantly associated with male sex, having a deceased or absent father, and maternal report of IPV. Among CHEU, *in utero* exposure to efavirenz (EFV)-based regimens during pregnancy was associated with lower gross motor scores compared to DTG-based regimens. (**Chapter III**) Latest evidence from a scoping literature review suggests that perinatal HIV and ART exposure can biologically influence child neurodevelopment through altered immune function, structural brain integrity, systemic inflammation, and growth faltering. There are limited data on the roles that social and behavioral factors play in promoting child neurodevelopment among families affected by HIV in SSA.

Conclusion: Relationship dissolution commonly occurs among couples affected by HIV, for a myriad of reasons. It is imperative to improve counseling messaging and better support people living with HIV who may experience IPV, relationship conflict, and separation from their partners, particularly during the vulnerable periods of pregnancy and postpartum. Additionally, IPV and paternal absence in the first year of life were significantly associated with poorer child neurodevelopment, regardless of maternal HIV status, and will require harmonized approaches to address and mitigate risk of delays. Despite evidence that CHEU have unique biologic and social factors that may influence their brain maturation, immune system, and overall health and wellbeing, we did not find a statistically significant difference in 1-year neurodevelopment between CHEU and CHUU. The lack of neurodevelopmental difference between CHEU and CHUU in this cohort, despite several sociodemographic differences, could be potentially attributable to the wider spread and more prolonged use of newer maternal DTG-based ART regimens during pregnancy and breastfeeding; prior studies have been unable to assess these improved regimens which are better able to sustain viral suppression and improve maternal health, so additional research is needed to validate this finding. There is an urgent need for rigorous, multidisciplinary research to identify modifiable aspects of biologic and household exposures that impact child neurodevelopment, as well as clear referral pathways for children, caregivers, and providers in need of additional support.

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ACKNOWLEDGEMENTS

Where do I even start?
With gratitude so grand –
Before I depart,
With my degree in hand...

THANK YOU, ASANTE SANA, WEEBALE:

To all of our **study's kiddos**,
And their **mamas and papas**:
Through research's ebbs and flows,
What an adventure it all was!

To our incredible **study teams**,
In Uganda and Kenya,
The collaborators of my dreams,
Couldn't have done it without ya.

To the **Obumu team in Uganda**:
Your imprint on me is forever evident,
You have the jokes and wits of a mamba,
And the loving hearts of an elephant.

I'm counting down the days till I can return.
Andrew, Agnes, Faith, Julie, Goretti, Paul:
From each of you, I have much more to learn.
And don't worry, I'll bring the soccer ball!

To the **HOPE team in Kenya**:
How lucky am I to work with you.
Like a bouquet of fragrant gardenia,
There is absolutely no sweeter crew.

Dalton, Hellen, and Maureen:
You tackle research with such graceful ease.
And there is nothing sweeter to glean,
Than your abundant love for our study's babies.

To my exceptional, outstanding chair, **Grace**:
You are so much more than my advisor,
Inspired by you, in everything I face,
I aspire to be like you: forever wiser.

To my incredible mentor, **Connie**:
You've taught me so much, got me in the door,
Five years and counting as your mentee
And hopefully a lifetime more.

From a magic deck of cards, **Mary and Kate**:
How lucky was I to get you Aces of Spades?
Together, you got me out of the gate... so we could
Weave together UW, Harvard, and UNAIDS.

Noel, Hilary, Anjuli, Irene, Rich, Monisha, Jen:
you've set the bar so high, my lanterns in the sky.
On this path that you anoint,
Thank you for guiding me to this very point.

To **my dearest parents, Ann and Marc**,
My absolute greatest role models,
You've kindled my each and every spark,
Ever since I was in swaddles.

You showed us the world,
And taught us everything we know.
From the epidemiologic wisdom you've pearled,
To the core values you breathe and bestow.

Thank you for raising us in Zambia,
On dumplings and Belgian stew,
Chasing constellations, lions, and hyenas.
I dedicate my dissertation to the both of you.

To my big bro, **Philip**:
You're always there to boost my morale,
I will never stop following in your footsteps,
Because I couldn't imagine a better pal.

To my best friend and (now!) husband, **Mitch**:
Words cannot describe, you are my everything.
And after all you've heard me talk about epi...
You deserve your very own degree.

To my three year old puppy, **Maui**:
My adventure buddy since the 1st day of PhD.
Thanks for always reminding me,
That there's much more to life than to study.

To my incredible **friends**:
We cheer each other on and lift each other up,
We share our lives through our unique lenses,
I can't thank you enough for always filling my cup.

To **UW students, faculty, and staff**:
The vibrancy of our learning culture is elite.
You taught me everything from reading a graph,
To grilling salmon at just the right heat.

I'll never forget this very special time,
That I had to learn and grow with all of you,
Sorry to say this all in a cheesy rhyme...
But every word could not be more true.

INTRODUCTION

Prevention of mother-to-child transmission programs (PMTCT) over the last decade have greatly improved access to HIV testing, counseling, and treatment for pregnant women living with HIV (PWLHIV) in sub-Saharan Africa (SSA). PMTCT programs have contributed to averting tens of millions of new infant HIV infections, more than halving the number of vertical transmissions between 2010 and 2020.¹ Despite this progress, gaps remain in women's long-term engagement with care during pregnancy and postpartum.^{2,3}

Strong partnerships between PWLHIV and their male partners may be associated with long-term engagement in PMTCT programs and improved maternal and infant HIV outcomes.⁴ Fathers play an essential role in family dynamics, resources, and child health and development; however, men are underrepresented in clinical services, and their voices are seldom captured in research.⁵ PWLHIV's male partners of unknown HIV status are especially important to test for HIV due to their high risk of acquisition.^{6,7} Paternal involvement in antenatal care (ANC) may improve birth outcomes, parental satisfaction, maternal engagement with PMTCT care, and child growth and development.^{4,5,8-13}

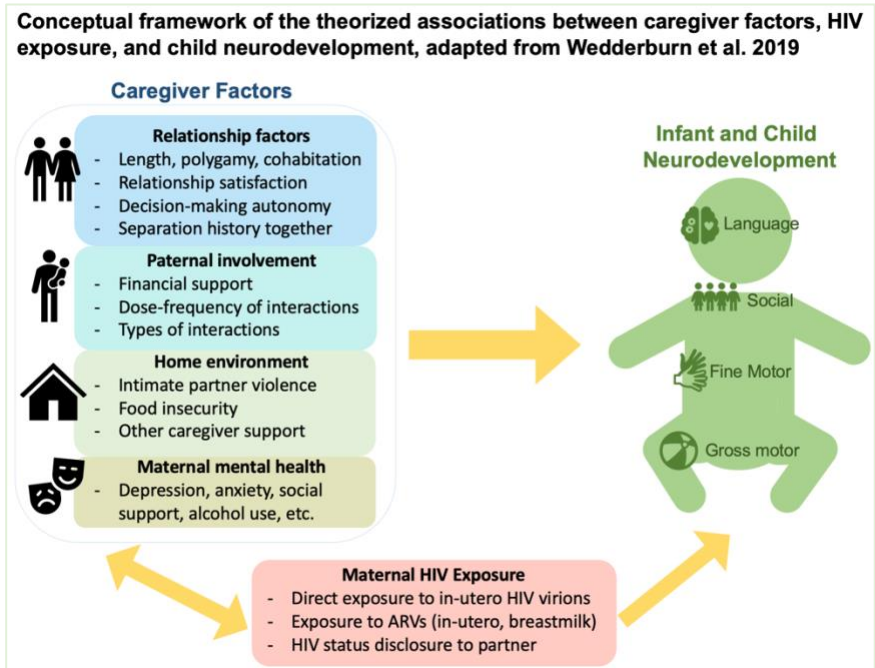
Relationship dissolution during pregnancy and postpartum can leave PWLHIV and their children vulnerable to financial hardship and poorer physical and mental health.¹⁴ Couples affected by HIV experience high risk of separation, and it is estimated that separation occurs five times more often in HIV-serodifferent couples where a female is living with HIV compared to couples in which a male is living with HIV.¹³ Women living with HIV are often diagnosed during pregnancy, and thus, during this period, an HIV diagnosis can leave PWLHIV particularly vulnerable to intimate partner violence (IPV), financial hardship, and abandonment,^{14,15} which are the most cited reasons PWLHIV avoid disclosing their HIV status to their male partners.^{16,17} These issues may be amplified in the context of polygamy. We conducted this research in Uganda, where polygamy is a common, legal, and socially accepted practice.

Maternal wellbeing is associated with improved health outcomes among children, regardless of a child's HIV status.¹⁸ The success of PMTCT programs over the last decade has led to a rapidly growing population of nearly 16 million children who are HIV-exposed uninfected (CHEU) around the world, with an additional one million born every year in SSA.^{19,20} In several countries in SSA with high HIV burden, the population of CHEU accounts for over 20% of children ≤14 years of age.¹⁹ Despite living "HIV-free", 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.²⁰⁻²⁸

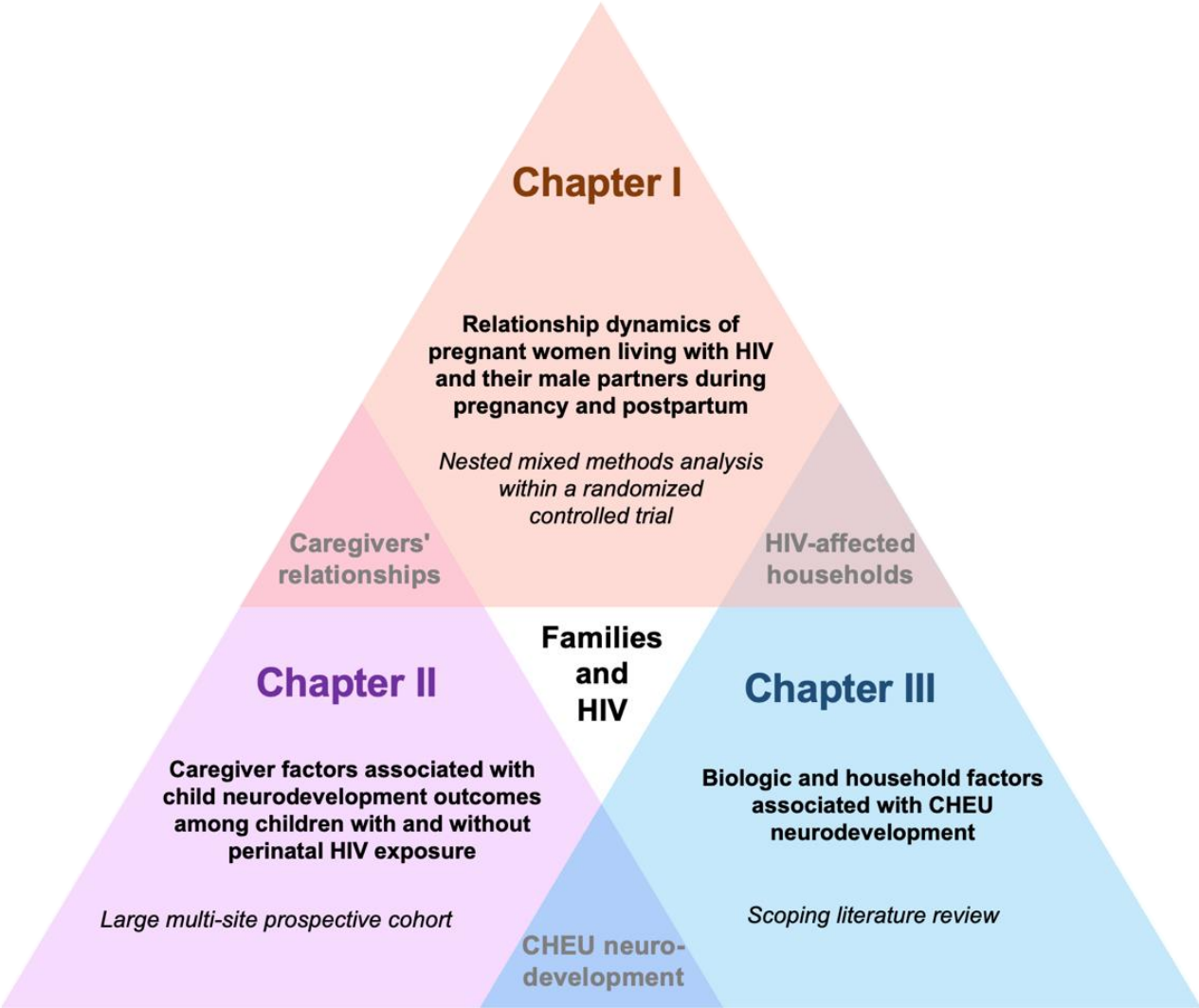
Most, but not all, studies have found increased risk of neurodevelopmental delays in CHEU compared to children born HIV-unexposed uninfected (CHUU). Previous studies are limited by inconsistent study designs, small sample sizes, only relying on one time-point for outcome measurement, and differences in ART exposures. Preterm birth, in-utero ART exposure, heightened maternal viremia during pregnancy, and early child inflammatory markers have all been shown to impair CHEU neurodevelopment in the first years of life.²⁹⁻³¹ Studies have noted differences in language, social and motor skills, brain composition and structure, and altered cell-mediated immunity between CHEU and CHUU.^{27,32,33} While the biologic etiologies of neurodevelopmental outcomes among CHEU are increasingly being studied using robust research strategies, less clear are the modifiable, social and behavioral pathways that synergistically increase risk of poor neurodevelopmental outcomes.

Kenya is home to nearly 1 million CHEU for whom research is urgently needed to identify modifiable caregiver and home factors to reduce the risk of suboptimal child neurodevelopment.¹ Mothers living with HIV tend to experience higher rates of IPV and poorer mental health outcomes, which could affect their ability to interact responsively with their children and promote healthy early development.³⁴⁻³⁶ Child exposure to household violence can severely impair neurodevelopment, but has yet to be evaluated among CHEU.³⁷⁻³⁹ A longitudinal cohort in South Africa found caregiver depression significantly mediated the relationship between caregiver HIV burden and poorer neurodevelopmental outcomes among older children^{35,36}, and a study in rural Kenya found caregiver stress, anxiety, and depression were all independently associated with poor child behavioral outcomes by age 4.⁴⁰ It is critical to assess whether,

and to what extent, HIV and ART exposures, maternal mental health, paternal involvement, and household violence are associated with poorer child neurodevelopment. Characterizing these factors associated with neurodevelopmental delays among CHEU within the first year of life can help identify specific groups of mothers and infants to target for enhanced monitoring, counseling, and support.



Chapter I of this dissertation identified factors associated with separation between PWLHIV and their male partners and assessed women’s PMTCT outcomes, such as maternal ART adherence and virologic suppression, through a nested mixed methods analysis within a randomized controlled trial. **Chapter II** compared 1-year neurodevelopment between Kenyan CHEU and CHUU in a large prospective cohort and identified caregiver and ART-related factors associated with poorer neurodevelopment among CHEU. **Chapter III** was a scoping literature review of the biologic and social mechanisms through which perinatal HIV exposure could impact early neurodevelopment among CHEU and summarized the key findings in a short commentary intended for researchers, healthcare providers, and policy makers.



OVERVIEW OF STUDY INVOLVEMENT

This dissertation was conducted within the robust infrastructures of two outstanding research studies: the Obumu Study in Uganda (PI: Connie Celum) and the HOPE Study in Kenya (PI: Grace John-Stewart). I have been fortunate to be involved in both studies in various capacities, which all greatly enriched my experience, learning, and skills development. I look forward to presenting this collective body of work in an invited talk at the 2023 International AIDS Conference held in Brisbane, Australia.

CHAPTER I: OBUMU STUDY

I have worked on the Obumu Study for five years, receiving close mentorship from Drs. Connie Celum and Andrew Mujugira. While embedding my MPH thesis and PhD dissertation work within the Obumu Study, I engaged in various forms of study involvement and learning. From Seattle, I supported study coordination, data management, reporting, analysis, and manuscript preparation. I spent the summer of 2019 working at the Kitebi Health Centre in Kampala, Uganda, where I assisted our study team with primary data collection of epidemiologic and micro-costing data, development of peer support groups for mothers living with HIV, and interviewing study participants, healthcare providers, and peer mothers (mothers with HIV who counsel newly diagnosed mothers). I learned about the Ugandan health system and the context of cultural and gender norms from my extensive conversations with our Obumu nurses, peer mothers, Ugandan Ministry of Health officials and the UNAIDS Country Director. Made possible by the exceptional guidance from my mentors and colleagues, I have led quantitative, qualitative, mixed methods, and costing analyses for publication for this and related studies. Most recently, I have been involved in training Obumu nurses on performing mixed methods analyses and manuscript writing.

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6. Nakyanzi A, Bulterys MA, et al. “Mixed methods analysis of point-of-care HIV viral load testing in Uganda”. (In preparation)

CHAPTER II: HOPE STUDY

I am tremendously fortunate to have been involved in the HOPE Study since its establishment, working closely with Drs. Grace John-Stewart, Irene Njuguna, Anjuli Wagner, and Maureen Kinge. Prior to the study launch, I supported the development of IRB submissions, study protocols/SOPs, training materials, questionnaires, and REDCap data collection tools. I served as the study data manager, responsible for developing our dynamic dashboard for automatic data reporting, R scripts for data management and

quality control, and leading data analyses for dissemination. For my dissertation, I worked most intimately with our child neurodevelopment data, to develop the R code to score child assessments, ensure rigorous quality control, and identify ‘red flags’ for nurses to refer children in need of more comprehensive testing. In anticipation of my postdoctoral training, we submitted two successful administrative supplemental grants to conduct sub-studies within the HOPE Study in Kenya and the FLOURISH Study in Botswana (PI: Kathleen Powis, Harvard), to allow us to conduct mixed methods and photovoice research focused on parental relationships, paternal involvement in caregiving, and child neurodevelopment.

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CHAPTER III: Neurodevelopment of children exposed to HIV

As a part-time consultant with the UNAIDS data team, under close mentorship by Drs. Mary Mahy and Kathleen Powis, I analyzed and developed figures of UNAIDS global data indicators of children who are HIV-exposed uninfected. These figures have been presented at the 2021, 2022, and upcoming 2023 International AIDS Society/CIPHER’s Annual Workshop for Children with Perinatal Exposure. For my final chapter of my dissertation, I partnered with Drs. Grace John-Stewart, Kathleen Powis, Mary Mahy, Laurie Gulaid (UNICEF) and Catherine Wedderburn (University of Cape Town) to write a commentary on the biologic and social factors contributing to child neurodevelopment among children with HIV exposure.

1. Bulterys MA, Mahy M, Powis K, Wedderburn C, Gulaid L, John-Stewart G. “Commentary on the neurodevelopment among HIV-exposed-uninfected children”. (Invited for the ***Journal of International AIDS Society’s Special Issue*** on Children Exposed to HIV, to be published in November 2023)

Other study involvement during graduate training

In addition to the above studies, I have been a part of other manuscripts during my graduate training:

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CHAPTER I: MIXED METHODS ANALYSIS OF RELATIONSHIP DISSOLUTION AMONG UGANDAN COUPLES AFFECTED BY HIV DURING PREGNANCY AND POST-PARTUM

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Published Citation:

*Bulterys MA, Mujugira A, Nakyanzi A, Wyatt MA, Kamusiime B, Kasiita V, Kakoola GN, Nalumansi A, Twesigye C, Pisarski E, Sharma M, Boyer J, Naddunga F, Ware NC, Celum CL. "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 and Behavior.** 2022; 10.1007/s10461-022-03910-3.*

ABSTRACT

High rates of relationship dissolution among pregnant women living with HIV (PWLHIV) and their male partners might increase mothers' and children's vulnerability to financial hardship and poor health outcomes. This mixed methods analysis identified factors associated with separation between PWLHIV and their male partners. We utilized data from a randomized controlled trial (www.ClinicalTrials.gov NCT03484533) of 500 PWLHIV attending antenatal clinics in Uganda and 236 male partners between 2018-2020 and followed until 12 months postpartum. Multivariate regression models estimated the impact of relationship factors on the adjusted relative risk of separation during follow up. We conducted in-depth interviews with 45 women and 45 men enrolled in the trial. Overall, 23% of PWLHIV reported separation during the study period. HIV serodifferent status, financial burdens and gender expectations were sources of relationship conflict. Significant factors associated with separation included unmarried, non-cohabitating, shorter, polygamous relationships, as well as HIV non-disclosure and verbal abuse. Participants discussed potential positive and negative consequences of separation, including impact on their mental health, treatment continuation, financial security, and safety. Addressing relationship dynamics is essential to improve counseling messaging and support PWLHIV who are experiencing relationship conflict.

INTRODUCTION

Engagement of pregnant women living with HIV (PWLHIV) in prevention of mother-to-child transmission (PMTCT) programs and long-term treatment continuation remain global priorities for HIV prevention.¹⁻⁴ Starting from conception, greater male partner involvement is associated with improved birth outcomes, parental communication, maternal mental health, and child development.^{4,5,8-11} PWLHIV face unique challenges, particularly when newly-diagnosed with HIV during pregnancy, and often avoid HIV status disclosure to their male partners due to fear of abandonment.^{14-17,41-46} Relationship dissolution during the vulnerable periods of pregnancy and postpartum could impact women's PMTCT retention, and consequently maternal and infant outcomes.^{4,5,12-14} Furthermore, relationship dissolution could impact women's financial stability, wellbeing, and ability to support their children.¹³⁻¹⁵ Compared to men, women in SSA tend to experience disproportionate burdens after separation due to a variety of systemic and cultural factors, including financial hardship, childcare responsibility, and stigma.^{47,48} Factors associated with relationship dissolution between PWLHIV and their partners, and the impact of separation on women's PMTCT outcomes (i.e. maternal antiretroviral treatment [ART] adherence and virologic suppression), remain under-explored areas.

HIV-affected couples face three-to-four times higher risk of relationship dissolution compared to the general population, and couples in which the female is living with HIV separate five times more often than couples in which only the male is living with HIV.¹³ HIV status disclosure comes with opportunities and challenges; counseling messages are often centered around encouraging disclosure between partners to build mutual support and encourage HIV testing, treatment and prevention. Paradoxically, HIV status disclosure by women living with HIV to their partners has been found to significantly increase likelihood of separation, particularly in cases of serodifferent HIV status.^{13,24,25} Qualitative studies describe disclosure avoidance to reflect both men and women's fear of receiving blame for bringing the virus into the relationship.⁴⁹

The perspectives of male partners of PWLHIV are underrepresented in both clinics and in research, but are important to capture due to their high risk of HIV acquisition and influence on relationship stability and partners' treatment continuation.^{6,7,12,13} Despite the important roles men play, ANC clinics are rarely tailored for male engagement.⁵⁰⁻⁵² Additionally, men commonly have HIV-stigmatizing attitudes,⁵³ and are less likely than women to seek HIV testing and treatment, leading to poorer clinical outcomes.⁵⁴⁻⁵⁹ Qualitative studies have described how male cultural and gender norms can affect all steps along the HIV care cascade, as undergoing HIV testing may threaten their sense of strength, and learning they or

their partners have HIV can impact their reputation, self-esteem, and perceived position as the family head.^{60,61} Mixed methods investigation is needed to identify male partner factors that impact relationship dissolution, and confirm that quantitative findings are rooted in lived experiences. This analysis aimed to identify factors associated with relationship dissolution between PWLHIV and their male partners, and potentially positive and negative consequences of separation. Results can identify PWLHIV at high risk of relationship dissolution, improve counseling messaging, and inform targeted prevention strategies for male partners.

METHODS

Study Population

Obumu enrolled 500 PWLHIV accessing PMTCT programs in Kampala, Uganda between 2018-2020 and randomized them 2:1 to receive an HIVST kit or a standard clinic invitation letter to deliver to their male partners (www.ClinicalTrials.gov NCT03484533). Eligibility criteria included PWLHIV ≥ 18 years old who were in a partnership, did not know their partner's HIV status, and were at low risk of physical IPV based on the World Health Organization's standardized screening tool for clinical diagnosis of IPV.⁶² PWLHIV delivered the HIVST kit or invitation letter to their male partners and encouraged them to enroll in the Obumu study, describing it as a study for pregnant women receiving antenatal care and their partners. PWLHIV then contacted the study nurses and described the information they shared with their male partners (including whether disclosure occurred), how the interaction went, and how they wanted the nurses to handle their case. For example, some PWLHIV asked study nurses to facilitate couples testing and disclosure, while others requested their HIV status remain confidential; no HIV status disclosure by a study nurse occurred without explicit permission from study participants. Male partners who enrolled in the Obumu study received general health information, provider-administered HIV and syphilis testing and, depending on results, linkage to HIV care or prevention. The primary aims of Obumu were to evaluate the effect of the intervention on 1) male partner's testing and linkage to HIV pre-exposure prophylaxis (PrEP) or ART, depending on his status, and 2) women's postpartum ART continuation and viral suppression at 12 months post-partum.

Nested Analysis

This mixed methods analysis nested within the Obumu trial drew on both quantitative and qualitative data to develop a set of concepts characterizing factors associated with relationship dissolution, factors associated with staying together, and consequences of separation. Convergent parallel triangulation was

used to simultaneously collect and analyze quantitative and qualitative data, and as a product of this study design, some concepts were only captured using one method.

Data Collection

PWLHIV and male partners were followed every 3 months until the female partner reached 12 months postpartum. Relationship characteristics (e.g., length of relationship, polygamy, marriage, living together, number of children, partner support) were collected at baseline, and HIV disclosure and separation status were captured at each visit. At the last study visit, PWLHIV provided blood samples for HIV viral load testing and were asked to self-report their ART adherence in the past 30 days using a Likert scale (responses ranged from excellent, very good, good, fair, poor, to very poor). The binary outcome “poor ART adherence” was defined by responding fair, poor, or very poor to this question, and lack of viral suppression was defined as ≥ 200 copies/ml. PWLHIV were asked to rank how supportive their male partner was using the following options: extremely, very, somewhat, or not supportive. Relationship satisfaction was measured among the first 174 PWLHIV enrolled using the Dyadic Adjustment Scale at baseline.^{63,64} A purposive sample of 45 PWLHIV and 45 male partners in Obumu, not necessarily in partnerships with each other, participated in a single in-depth interview (IDI). Purposive sampling captured a range of experiences with timing of HIV diagnosis, disclosure/non-disclosure, and length of relationships. Trained Ugandan qualitative researchers (AN, BK, CT, VK, GN) collected qualitative data through IDI which lasted approximately 60 minutes. A comprehensive qualitative interview guide probed women’s and men’s experiences with HIVST, relationship quality, and fears or experiences with HIV testing and disclosure. The topic of relationship separation was mostly discussed hypothetically, and in some instances, experientially. Women and men who stayed with their partners during the study period discussed factors that contributed to staying together, and individuals in relationships with conflict discussed factors that contributed to conflict or relationship dissolution. Interviews were audio-recorded, with permission, and were transcribed and translated verbatim from Luganda to English by the interviewer.

Data Analysis

Quantitative data were analyzed using R Programming (version 09.2, www.R-Project.org, Vienna, Austria). The main outcome was relationship dissolution reported at any study visit from pregnancy to 12-months postpartum. Descriptive statistics characterized the overall sample of PWLHIV at baseline, and multivariate log binomial regression models with robust standard errors estimated the impact of relationship factors on the risk of separating during follow up, adjusting for key confounders determined *a priori*, and presented as adjusted relative risks (aRR). Multivariate log binomial regression models also

estimated the impact of separation on maternal viral suppression and self-reported ART adherence at 12 months postpartum. Qualitative transcripts were imported into Dedoose (version 9.0, www.dedoose.com, SCRC, CA, USA) and were coded by EEP and JB. Twenty percent of transcripts were double-coded and compared for coding consistency. Discrepancies were resolved through discussion. MAB analyzed data inductively to identify emergent concepts, with guidance from NCW, MAW, CLC, and AM. Concepts were then organized into broad categories, such as obstacles that arise in relationships, factors that contribute to relationship satisfaction, and reasons why some couples overcome these obstacles. Relevant quantitative and qualitative data were then integrated, resulting in a final set of interpretations.

Ethical Approvals

This study was approved by the University of Washington Human Subjects Review Committee (STUDY00002257), the Ugandan National HIV/AIDS Research Committee (NARC 200), and the Uganda National Council for Science and Technology (SS 4501). All participants provided written informed consent.

RESULTS

Pregnant women living with HIV (*Table I*)

Five hundred PWLHIV enrolled, of whom 115 (23%) reported separating with their partners during the study period. The median ages of PWLHIV and their male partners were 27 years (IQR: 23-31) and 32 years (IQR: 28-36), respectively. Approximately 33% women had fewer than seven years of schooling. Most (95%) women were married to their partners, and 42% had been together for over four years. Approximately 30% of women reported their partnership was polygamous. Almost half of women were newly diagnosed with HIV during their current pregnancy, and 68% had not disclosed their HIV status to their partners at the time of enrolment.

Male partners (*Table II*)

Almost half of the 500 PWLHIV's male partners enrolled in the study (N=236) with confirmatory HIV testing through the study staff, of whom 21 (9%) reported separating with their partners during the study period. Approximately 35% had fewer than seven years of schooling, and 98% were employed. Almost all enrolled men were married, and 24% reported their partnership was polygamous. At enrolment, 22% of enrolled men tested HIV-positive. Overall, 58% of men knew their female partner had HIV, 15% thought their partner was HIV-negative, and 27% reported not knowing their partners' status.

Qualitative sample (Table III)

The qualitative study involved 90 participants, 45 PWLHIV and 45 men, with median ages of 27 and 31 years, respectively; 18% percent of men were living with HIV. At the time of the IDIs, over half (53%) of PWLHIV had disclosed their HIV status to their male partners, and 29% of men knew their female partner had HIV. Six women and two male partners captured in this qualitative sample reported separating from their partners during the study.

FACTORS ASSOCIATED WITH SEPARATION (Figure I)

Relationship factors

Unmarried, not cohabitating, and together less than a year

Relationship separation was associated with being unmarried (aRR=6.16, 95% CI: 2.07-18.3, $p<0.01$), not cohabitating (aRR=4.38, 95% CI: 1.94-9.90, $p<0.01$), or in a relationship for less than a year (aRR=3.19, 95% CI: 1.44-7.08, $p<0.01$), compared to relationships lasting four or more years (Table I).

Polygamy

Polygamy was more common among couples that separated than those that stayed together (43% vs. 25%) and was significantly associated with double the risk of separation (aRR=2.07, 95% CI: 1.18-3.62). A few women in polygamous relationships were captured in the qualitative sample, and reported feeling unhappy, disrespected, and devalued by their partner.

Relationship dissatisfaction

Female report of an “unsupportive” partner was significantly associated with separation (aRR=4.07, 95% CI: 1.81-9.14, $p<0.01$). In sub-analyses of relationship satisfaction with 174 women, those who regretted entering the relationship had an 8.5 times higher risk of separating (aRR=8.54, 95% CI: 2.90-25.2, $p<0.01$), and frequent quarrels were associated with almost 4 times higher risk of separating (aRR=3.71, 95% CI: 1.1-12.3, $p=0.04$). On a Likert scale ranking the future of their relationships, significantly more of the women who eventually separated with their partners reported the extreme outcome – “My partnership can never succeed, and there is nothing I can do to keep it going” – compared to women who stayed together (19% vs. 1%). Similarly, men who reported feeling unhappy in their relationships at enrollment faced a 16-fold higher risk of separation (aRR=16.04, 95% CI: 4.24-60.7, $p<0.01$).

HIV status disclosure and serodifference

Women feared HIV disclosure would lead to abandonment or abuse

HIV status non-disclosure at baseline was associated with three times higher risk of separating (aRR=2.97, 95% CI: 1.57-5.60, p<0.01). Some women who feared abandonment preferred to wait to disclose their HIV status until after delivery; however, non-disclosure by the time of delivery was associated with double the risk of separating (aRR=2.00, 95% CI: 1.54-3.87, p<0.01). When examining the subset of women who had not disclosed prior to study enrollment, disclosure during the study was not statistically associated with separation.

[Interviewer: Why do you think you did not want him to know your HIV status?] “I knew he was going to leave me.” PWLHIV, 23 years old, undisclosed

Women perceived abuse to be a likely consequence of having different HIV status (serodifference):

“If he gets to know that he is HIV negative and I am HIV positive, the way he is very tough and stubborn, we could have had a huge disagreement...My partner is naturally tough, he is a kind of person who could even decide to injure me or [do] something. He keeps saying that he comes from very far, he can kill me or do something bad.” PWLHIV, 36, undisclosed

Approximately 11% of all women reported they experienced verbal abuse (threats) from their partners in the year preceding the study, and verbal abuse during the study was associated with three times higher risk of separation (aRR=2.78, 95% CI: 1.03-7.50, p=0.05).

Some men validated women’s fears about discovering serodifference, and described the stigma associated with knowingly staying with a person living with HIV (“*Personally, I think that I let her go in case I am negative and she is positive. I separate from her*”). These men felt so strongly to the point of considering self-harm (“*I thought about taking poison so I can die and not live in shame of staying with an infected person*”).

Male partners feared contracting HIV, leading to lost sexual “appetite” and distrust

Among HIV-negative men, 64% worried about getting HIV, and high levels of worry were more common among men who eventually separated with their partners (36% vs. 25%). These men stressed about the “*anticipation of waking up one day when you have also contracted the virus,*” and blamed their wives for putting them at risk (“*I labeled her as a murderer because she had brought for me HIV*”, HIV-negative male). There was common lack of awareness and/or confidence in the U=U principle

(unsuppressed=untransmittable), as men did not believe that their partners' ART adherence could truly protect them from contracting HIV. Fears and blame drove men to distrust, resent, and ultimately want to separate with their partners.

"My wife told me that if she adheres well to her drugs then she can't infect me. I didn't believe what she told me and I said to her "If it is death, then you have surely killed me." HIV-negative male, 32

The discovery of serodifference led to changes in the relationship (*"it is different from the way it used to be"*), particularly in the loss of sexual intimacy (*"the sexual appetite I had just goes away"*). Whether this was due to decreased attraction or fear of acquiring HIV, or a combination of several factors, the decline in sexual intimacy interfered with communication, intimacy, and the sense of connectedness. This was reflected in quantitative data, as higher numbers of reported sexual acts with female partners in the prior month was significantly associated with reduced risk of separation (aRR=0.96, 95% CI: 0.92-0.99, p=0.04). A few men accused their partners of wanting to deliberately infect them with HIV, based on their assumption that PWLHIV would feel more secure in their relationships if both partners were on treatment.

[Interviewer: "How would your wife feel if you contracted the virus?"] "What I know is that it could be her happiness [laughs], because she wants for both of us to be on medication." HIV-negative male, 28

Unmet gender expectations led to resentment

The Blame Game: "Poor" Husband, "Lazy" Wife

Serodifference may not have always been the main reason for separation, but it accentuated existing tensions. The presence of strong gender roles meant that unmet expectations led to resentment. Men resented their female partners if they were *"lazy"* and did not do household duties such as cleaning and caring for the children, and women resented their male partners if they did not provide financial support (*"As you know a man is supposed to leave money that supports the home, he has to take care of you."*). In unhappy partnerships, men and women questioned why the other was not meeting expectations, leading to dissatisfaction and frustration:

"I do not know where he puts the money, and that situation is hard on me. [...] How do you say you are working, and you fail to leave money at home for feeding?" PWLHIV, age 24, disclosed

Several men reported that their partner's "laziness" was the 'deal-breaker' (*"it is her only weakness, can be patient with the rest but not that"*). Whether this was truly the only deal-breaker for the relationship, or if it was a viable excuse for him to "check out" of an already failing relationship, is unclear.

Economic inequity (unequal power of finances) in the year prior and during the study was associated with separation, respectively by 5-fold (aRR=5.15, 95% CI: 1.10-24.14, p=0.04) and 11-fold increased risk (aRR=11.40, 95% CI: 2.94-44.5, p<0.01).

Male obligations to support the family

Since gender roles suggest that family planning is a "woman's job", men had little power in decision making, leading them to feel trapped when women conceived after giving the impression that they were on birth control. This, coupled with the gender expectation that men must support the family, drove men to feel powerless and resentful (*"nothing I could do about it"*).

Not every unhappy couple separated; oftentimes, they stayed together out of obligation for "*the sake of the children*". Sharing biologic children was protective of the relationship; having one child compared to none was associated with a 15% reduced risk of separation (aRR=0.85, 95% CI: 0.72-0.99, p=0.04), but was no longer significant after adjusting for maternal age, education, and marital status (aRR=0.95, 95% CI: 0.72-1.23, p=0.68). Fathers were concerned for their children's needs (*"a child needs parental love"*) and feared losing access to them (*"I cannot separate with her, or she would take my kid"*). Men also feared judgement from society if they stopped supporting their families, leaving them feeling trapped in the relationship:

"We are together now I think because of the children. [...] If she goes by herself I will be very happy, but I fear to tell her by myself that she should go because I fear to be imprisoned. I am telling you I pray to God about it. I pray that one day she sees me as someone who is worthless, someone with no good future so that she just leaves me. [...] But when I think about the children... I keep lying to her that I will stay with her but I really do not know. You never know but...since I have produced children with her..." HIV-negative male, age 39

One man who wished to "*separate in good faith*" saved money to continue supporting the family while living separately, so he could regain his independence and live as a "*bachelor*".

“I will take PrEP until I get money and rent out a house for her, we separate in good faith and I continue supporting her, I will put up a situation that can benefit us both.” HIV-negative male, age 23

POSSIBLE CONSEQUENCES OF SEPARATION (Table IV)

Treatment outcomes

Among the 439 PWLHIV with viral load data at follow up, 47 (11%) were virally unsuppressed; 15% among those who had separated with their partners, and 9% among those who had stayed together (Table IV). Additionally, 13 (3%) reported poor ART adherence at follow up, 6% among those who separated with their partners, and 2% among those who had stayed together. There was a trend between separation and reporting poor ART adherence (aRR=3.33, 95% CI: 0.99-11.28) or being virally unsuppressed (>200 copies/ml; aRR= 1.42, 95% CI: 0.69-2.92) around 12 months postpartum, but these associations were not statistically significant.

Many women described their fear of their partners disclosing their HIV status to the community upon separation. Women who experienced separation and unwanted disclosure described its negative toll on their mental health (*“He starts telling the people he has already found me sick... He throws [my HIV status] in my face which makes me feel bad”*). One woman described that she would have stopped adhering to her HIV treatment if it weren't for her children:

“[After separation,] I felt bad, I felt bad and if I did not have these children, I would have stopped taking the medicine (ARVs) because he went on telling everyone everywhere how I am infected with HIV and I felt I did not have any peace nor did I have any friend on the village.” PWLHIV, 22 years, disclosed

Financial hardship

Women reported feeling concerned that separation would lead to financial insecurity, particularly the inability to afford basic necessities like food and housing:

“[Separation] means I will suffer with my children... it means I will not have money to look after me and the baby, I will not have money to pay rent”. PWLHIV, 23 years old, undisclosed

Motivation to work and have financial independence

While some women feared separation would lead to financial hardship, other women deliberately chose to separate with their partners, and saw separation as an opportunity to become financially independent (*“it is now about working and looking after myself”*).

“The stress reduced when I had left [him] and started working - I had some peace as I would go and work and get something to eat and in time and even eat what I wanted.” PWLHIV, 22 years, disclosed

“When I told him [I have HIV], he became angry... He got another woman where he would stay and a time came and he stopped coming back home. He was also not providing for me, he got disorganized like all men do and we really got misunderstandings and because of that I decided to take some rest from the marriage. When [I left him], I started thinking and looking here and there and that is how I got that small job that I am doing. A time will come and we shall separate completely because he shows me that he is no longer interested in me so it is now about working and looking after myself. I did not just sit and I continued working till I started my own business.” PWLHIV, 24 years, disclosed

Finding safety after escaping abusive relationships

Multiple women described their experiences with abuse in past or current relationships, and a few women recounted the moment they decided to separate with their abusive partners:

“You see the father of my other child had HIV and he was okay to be with me but he used to beat me and I decided to separate from him. [...] The challenge that led to our separation was because he used to fight with people in bars and from there he would want to transfer that anger on me. I had stayed with him for five years. I persevered until I decided to leave before I die because one day, he got a [weapon] and wanted to kill me with it.” PWLHIV, 23 years old, undisclosed

FACTORS ASSOCIATED WITH STAYING TOGETHER (Figure II)

Mutual love and support

Love and monogamy contributed to improved commitment to the relationship. While some women avoided disclosing their status, some PWLHIV immediately disclosed to their partners following diagnosis. They wished to protect their male partners by encouraging them to test, treat or prevent infection. Hiding their status *“would have been so much of a burden, could not even handle it”*.

Men in loving relationships initially assumed that if his wife was living with HIV, he too must have HIV. This acceptance of potentially living with HIV shaped a sense of empathy and solidarity (“*I was ready for anything*”, “*I would have taken tablets like her if I was positive*”), and recognizing that she would have supported him in return. Men experienced disbelief when they first tested HIV-negative, as exemplified by asking health workers to re-test them. Once these men realized that they were indeed in a serodifferent relationship, they did not treat their partner living with HIV any differently (“*I still treat her the way I used to treat her before I got to know that she is HIV positive*”). Men felt a strong duty and responsibility to stay together and support their partner’s ART adherence.

“I thought he will abandon me after finding I have HIV [...] however he did not. He just gave me courage [...]. He told me that the most important thing is for me to take my ARVs well so that I can live longer to look after our children together with him.” PWLHIV, 32 disclosed

Teamwork

There is a strong sense of teamwork among couples committed to staying together (“*We survive in all situations for as long as you understand each other and each of us knows the other’s problem so we share the little that we get*”). In contrast to couples who resented each other for unmet gender expectations, men in committed relationships supported their wives by taking on traditional female roles when necessary (“*We support each other. [When she is sick] I wake up early to make her porridge and wash the clothes*”), and women worked together with their partners to provide for the family. This teamwork alleviated gendered pressures on one another and encouraged the pair to tackle obstacles such as housework and finances “*together as a couple*”.

Sense of Protection: from God and PrEP

Most HIV-negative men expressed fear of contracting HIV from their partners, so a sense of protection was important to their wellbeing. While many men reported lacking trust in their partners, some still felt protected from HIV. Men thanked God for “*saving*” them from contracting HIV up until that point, attributing their sustained HIV-negative status to “*God’s will*”. Men also accepted PrEP to protect themselves from HIV (“*I accepted to take it to save my life*”). They recognized that they would have separated with their partners if their virus was still “*active*,” but since the virus was “*asleep*” thanks to ART, the “*relationship continued as usual*” (Figure II). Additionally, HIV-negative men acknowledged that even if they were to leave their current partner, they would still be at risk of contracting HIV elsewhere.

“It could be God’s luck that you escaped that so if you stay with your partner, there are chances that you can still be safe. When you go out with one another, unless you [test her], chances are that you could be [infected] as well. But with a partner whom you already know her status and you can take precautions, why don’t you stay where you are?” HIV-negative male, age 38

DISCUSSION

This mixed methods analysis investigated relationship dissolution between pregnant and postpartum women living with HIV and male partners of unknown HIV status. Almost 25% of PWLHIV reported separation during the study. While some couples found HIV disclosure, serodifference, financial burdens and gender roles as sources of conflict, other couples approached these obstacles as opportunities to overcome together. Factors associated with separation included being in unmarried, non-cohabitating, shorter, polygamous relationships, as well as HIV non-disclosure, relationship dissatisfaction, infrequent sexual activity, unmet gender expectations, and abuse. Factors associated with staying together included HIV status disclosure, shared biologic children, monogamy, sense of love and support, and a teamwork mindset regarding gender expectations. Fear of HIV among HIV-negative male partners was apparent; men who felt protected in some way (e.g., U=U, PrEP, God) were more likely to stay with their partners. Participants discussed potentially negative and positive consequences of separation, including impacts on mental health, treatment continuation, financial security, and removal from abusive relationships. We found a trend of lower self-reported ART adherence and viral suppression among women who had separated from their partners, but these associations were not statistically significant. Separation may be harmful or beneficial to PWLHIV depending on the specific nature of their relationships, and further investigation is needed to explore this.

Qualitative studies cite women’s fear of abandonment to be the biggest barrier to HIV disclosure.^{14,15,17,65-67} Particularly during the pregnancy and postpartum, abandonment or abuse was seen to have critical social, economic, and health implications for women in this study. Women who experienced economic abuse had significantly higher risk of separating with their partners during the study; further studies are needed to assess economic dependency and potential repercussions when women lose financial support from partners. Since PWLHIV are especially vulnerable to abandonment, this study population of PWLHIV and male partners of unknown HIV status was well suited to capture couples at the greatest risk of separation.³⁷⁻³⁹ Few studies have assessed separation quantitatively among HIV-affected couples. Our observed prevalence of separation (23%) is consistent with that of six previous studies (15-34%) in low-

and middle-income countries (LMICs). These studies identified similar factors that were associated with separation: woman living with HIV (regardless of male partner's status), unmarried, not cohabitating, being a higher-order wife in a polygamous marriage, and household poverty.^{13,14,41,68-70} Though useful, many of these studies predated the pre-universal ART era and excluded "remote communities" or couples at highest risk of separating (i.e., they only recruited couples who were attending HIV testing services together and "planned to stay together for ≥ 2 years"). Additionally, these studies did not assess how separation impacted women's clinical outcomes.

We found the same relationship factors were associated with both separation and non-disclosure.⁴⁴ HIV status disclosure by women living with HIV to their partners has previously been shown to be associated with relationship dissolution;^{68,71} we also found HIV-negative men in unhappy relationships blamed their wives for putting them at risk of HIV, and feared the stigma of staying together. Interestingly, the quantitative analysis found an opposite association; non-disclosure was associated with a three times higher risk of separation. It is possible that women in our sample who chose to not disclose were already in unstable partnerships and felt at most risk of abandonment, and women who did disclose weathered the risk of separation because they felt more confident in the strength of their relationships. Persistent HIV stigmatizing beliefs among men could play a factor in some men's desire to separate with their partners after the discovery of serodifference. A mixed methods study in Tanzania found that among male partners accompanying their wives to antenatal care, young age, low education, and notions of toxic masculinity were associated with stigma towards people living with HIV.⁵³

Ugandan men can have multiple wives in a legal union, with over 8% of marriages nationally being polygamous.⁷²⁻⁷⁴ Approximately 30% of PWLHIV in this study reported polygamy, which was significantly associated with HIV non-disclosure, having an unsupportive partner, and separation.⁴⁴ PWLHIV noted that they felt insecure and devalued if their husbands called other wives in her presence, and feeling "dispensable" drove women to evade disclosure. Monogamy was protective of separation, as demonstrated by women in loving relationships disclosing immediately after being diagnosed with HIV, and their partners, in turn, showing support. The impact of polygamy on HIV disclosure warrants further investigation.

Fathers play a critical role in income generation, household resources and food security.⁸ Financial hardship is a salient threat to paternal mental health and family stability in resource-limited settings.^{75,76} Parental conflict is associated with depression and poorer child outcomes.^{15,45,46,77-80} This analysis found that unmet gender expectations in partnerships and financial burdens contributed to resentment. Abiding

to gender roles can be damaging in families and requires challenging deep-rooted, intergenerational gender structures.^{10,81} According to a South African study, fathers felt their fatherhood was limited to just being an “ATM machine” – support groups and campaign messaging are needed to empower men to redefine the possibilities of fatherhood.^{10,82}

PWLHIV experiencing IPV are at higher risk of treatment non-adherence.^{83,84} Women in this study were at low risk of IPV (based on screening prior to enrollment as an eligibility criterion), so may be underrepresented in this study. Compared to the 2-10% of our sample who reported any kind of abuse, an estimated 40% of Ugandan women ≥15 years had experienced physical, sexual, or psychological abuse within the last 12 months.⁸⁵ Presence of IPV doubled the odds of relationship dissolution in other studies.^{15,46} IPV is experienced by men and women; studies in South Africa and Uganda found over 40% of men reported also being victims abused by their female partners.^{75,86} Depression is associated with experiencing as well as perpetrating IPV,^{75,87-90} so challenging these attitudes may be necessary for improving maternal and paternal mental health. Successful violence-reduction programs like Rwanda’s national *Sugira Muryango* (Kinyarwanda for *Strengthen the Family*), a home-delivered intervention, have shown to reduce IPV and improve father engagement, mental health, relationship satisfaction, and child outcomes.⁹¹⁻⁹⁴

Relationship dissolution was not always a negative outcome. The process leading up to relationship separation can be long and complex, and influenced by societal pressures and expectations.^{95,96} Separation can offer an opportunity to invest in one’s self-growth, resilience, confidence, and improved physical and mental wellbeing.⁹⁷ This can be observed among Obumu women who describe feelings of long-awaited “peace” and newfound motivation for working post-separation. In attempts to avoid loneliness and isolation, relationship dissolution can also encourage individuals to lean on and expand their social support systems. For women experiencing physical, emotional, or economic abuse in their relationships, separation can protect against further traumas. Additionally, exposure to household violence impairs child development, and child outcomes can be improved by co-parenting rather than forcing parents to stay together with conflict.^{98,99} Care providers and peer counselors could support PWLHIV by recognizing the potentially positive benefits of separation and extending beyond the standard “disclose and stay together” counseling messages. Further studies are needed to disentangle these complex experiences to tailor the best guidance to individuals’ unique situations.

This analysis had several strengths. We leveraged an RCT with a large sample of PWLHIV in relationship with a partner of unknown HIV serostatus who had not recently tested. Given the complex and ever-

evolving nature of relationships¹⁰⁰, this mixed methods analysis achieved more than either quantitative and qualitative analyses could alone, by providing context and confirming associations were rooted in lived experiences. Because antenatal care is typically centered around mother and child, paternal voices are vastly underrepresented in research. Male partner perspectives were captured both quantitatively and qualitatively in this study.

This analysis was limited by selection biases. We sampled PWLHIV and male partners who agreed to participate in a randomized trial about secondary distribution of HIVST, which may not be reflective of the general population of couples. Only women in partnerships and who did not know their partners' HIV status were enrolled in the trial; therefore, women who experienced relationship dissolution because of HIV status disclosure prior to the trial were not captured; this oversampled undisclosed PWLHIV in relationships. We also excluded PWLHIV at high risk of IPV, therefore women more likely to experience negative consequences of disclosure or (including violence or arguments) may be underrepresented. Selection bias is also present in male partner enrollment. Since less than half of male partners enrolled in the study, men who came to the clinic, tested for HIV and enrolled in the Obumu study were likely in stronger relationships, as only 9% of enrolled men reported separation (compared to 23% of women). Enrolled men had voluntarily agreed to frequent HIV testing and discussions on sensitive topics. Men who refused HIV testing and clinic linkage, or who separated with their female partners already were missed, not capturing the perspectives of men who may be the most likely to separate with their partners. This was a controlled research environment (e.g., frequent study visits with engaged nurses, comprehensive counseling on HIV disclosure and relationship advice, peer support groups), so the proportions of women who disclosed their HIV status and stayed with their partners were likely higher than would be observed outside of the trial. Furthermore, differential misclassification bias arose if women who experienced separation were more likely to recall the exposures that contributed to their relationship separation. With parallel qualitative and quantitative data collection, some findings were only captured through one method, not both, limiting our ability to integrate and confirm findings across methods. We did not capture mental health, religious beliefs, separation history, and which partner initiated the separation.

Conclusions

Separation was frequent among PWLHIV and their partners. Relationship factors, HIV disclosure, serodifference, financial burdens and gender expectations influenced risk of separation. Our results can be used to identify PWLHIV at highest risk of separation: undisclosed women in unmarried, shorter, non-cohabitating and polygamous relationships with unsupportive or abusive partners. Our findings can be

used to inform interventions and tailor counseling messages. Addressing relationship dynamics is important to optimize health outcomes and identify women who will benefit from extra support. Counseling should extend beyond the “disclose and stay together” messaging and provide person-centered support to women who are not in positions to disclose or are in unhealthy relationships. Male partners play a central role in relationship stability and their representation in future HIV partner studies should be prioritized. Further research is needed to evaluate the impact of separation on women’s treatment outcomes.

Declarations

Conflicts of Interests

Dr. Celum has served as a scientific advisor to Gilead Sciences and Merck. The authors declare no conflicts of interest.

Funding Source

This work was supported by the US National Institutes of Health [NIMH R01 MH113434]. The funders had no role in study design, data collection, analysis, writing of the report, nor the decision to submit for publication.

Author Contributions

Authors MAB, AM, CC, and NW conceptualized the research question. CC, AM, AN, FN, MS, and JB led the quantitative research, and NCW, MAW and EEP led the qualitative research and supervised data collection and analysis. BK, VK, GNK, AN, and CCT collected the qualitative data. MAB analyzed the quantitative and qualitative data under guidance by CC, NW, and AM. MAB and CC drafted the manuscript with substantial input from NW, AM, MS, and EEP. All authors approved the final version.

Acknowledgements

We would like to thank the study team and the study participants. We acknowledge Dr. Karusa Kiragu, the Country Director of The Joint United Nations AIDS Program (UNAIDS) in Uganda, for providing her insight and expertise.

Data Accessibility

Quantitative and qualitative data may be made available by authors CC and NW, upon reasonable request.

CHAPTER I: TABLES & FIGURES

Table I. Descriptive characteristics of enrolled women, and regression models comparing women who did and did not separate with their partners

Baseline Characteristic	Overall, N = 500	Separated during study, N = 115	Stayed together, N = 385	Unadjusted RR (95% CI)	p	Adjusted RR (95% CI)	p
Education							
Secondary or higher (>13 years)	96 (19%)	20 (17%)	76 (20%)	Ref		Ref ^a	
Primary completed, secondary incomplete (7-13 years)	237 (47%)	62 (54%)	175 (45%)	1.35 (0.76-2.40)	0.30	1.40 (0.76-2.60)	0.28
Less than primary (<7 years)	167 (33%)	33 (29%)	134 (35%)	0.94 (0.50-1.74)	0.84	0.82 (0.39-1.73)	0.60
Not currently married (ref: currently married)	23 (5%)	11 (10%)	12 (3%)	3.38 (1.41-7.64)	<0.01	6.16 (2.07-18.3)^b	<0.01
Relationship type							
Husband, living together	436 (87%)	90 (78%)	346 (90%)	Ref		Ref ^b	
Partner, living together	23 (5%)	5 (4%)	18 (5%)	1.06 (0.39-2.95)	0.90	1.35 (0.42-4.39)	0.61
Partner, not living together	41 (8%)	20 (17%)	21 (5%)	3.65 (1.90-7.03)	<0.001	4.38 (1.94-9.90)	<0.001
Length of relationship							
≥ 4 years	210 (42%)	37 (32%)	173 (45%)	Ref		Ref ^c	
1-3 years	224 (45%)	52 (45%)	172 (45%)	1.41 (0.88-2.26)	0.15	1.63 (0.91-2.91)	0.10
< 1 year	65 (13%)	26 (23%)	39 (10%)	3.12 (1.69-5.74)	<0.001	3.19 (1.44-7.08)	<0.01
Relationship is polygamous	147 (29%)	49 (43%)	98 (25%)	2.24 (1.44-3.48)	<0.001	2.07 (1.18-3.62)	0.01
Fewer than 10 sexual intercourses in last month (ref: 10 or more)	433 (87%)	106 (92%)	327 (85%)	2.05 (0.99-4.29)	0.05	1.93 (0.92-4.06)	0.08
Maternal HIV diagnosis							
Mother did not know she had HIV before this pregnancy (ref: she did know)	292 (58%)	61 (53%)	231 (60%)	1.32 (0.97-2.02)	0.19	1.11 (0.65-1.88) ^c	0.70
Mother did not know she had HIV during last pregnancy (ref: she did know), among women who had a previous pregnancy	175/366 (48%)			1.64 (1.00-2.69)	0.05	1.57 (0.85-2.92) ^c	0.15
Undisclosed at baseline (ref: disclosed)	341 (68%)	96 (84%)	245 (64%)	2.89 (1.69-4.93)	<0.001	2.97 (1.57-5.60)^c	<0.001
Has her partner ever tested for HIV							
She thinks yes	133 (27%)	20 (17%)	113 (29%)	Ref		Ref ^c	
She thinks no	189 (38%)	50 (43%)	139 (36%)	2.05 (1.15-3.64)	0.01	1.83 (0.90-3.76)	0.10
She doesn't know	178 (36%)	45 (39%)	133 (35%)	1.91 (1.07-3.43)	0.03	2.36 (1.16-4.82)	0.02
How supportive is her partner							
Extremely supportive	94 (19%)	13 (11%)	80 (%)	Ref		Ref ^c	
Very supportive	244 (49%)	47 (41%)	197 (51%)	1.47 (0.75-2.86)	0.26	1.83 (0.82-4.10)	0.14
Somewhat or not supportive	162 (%)	55 (%)	107 (%)	3.16 (1.62-6.18)	<0.01	4.07 (1.81-9.14)	<0.001
No household income in last 3 months	13 (5%)	8 (7%)	15 (4%)	1.84 (0.76-4.47)	0.175	1.12 (0.36-3.49)	0.84
Reports abuse in year prior to enrollment							
Physical (slapped, kicked)	30 (6.0%)	7 (%)	23 (%)	1.00 (0.39-2.56)	0.10	1.39 (0.45-4.28) ^c	0.56
Forced sex	12 (2.4%)	2 (1.7%)	10 (2.6%)	0.66 (0.14-3.07)	0.60	1.08 (0.32-5.53)	0.93

Economic abuse (unequal control of finances and resources)	12 (2.4%)	6 (5.2%)	6 (1.6%)	3.47 (1.10-10.97)	0.03	5.15 (1.10-24.14)	0.04
Verbal (insults, threats)	53 (10.6%)	22 (19.1%)	31 (8.1%)	1.98 (1.02-3.87)	0.04	1.43 (0.64-3.21)	0.39
Reports experiencing abuse during study period							
Physical (slapped, kicked)	11 (2.2%)	4 (3.5%)	7 (1.8%)	1.95 (0.56-6.77)	0.30	1.45 (0.21-6.18)	0.87
Economic abuse (unequal control of finances and resources)	18 (3.6%)	13 (11%)	5 (1.3%)	9.68 (3.38-27.80)	<0.001	11.4 (2.94-44.45)	<0.001
Verbal (insults, threats)	24 (4.8%)	11 (9.6%)	13 (3.4%)	3.03 (1.32-6.95)	<0.01	2.78 (1.03-7.50)	0.05
Any other form of abuse	10 (2.0%)	6 (5.2%)	4 (1.0%)	5.24 (1.45-18.9)	0.01	4.65 (0.75-28.9)	0.09
Continuous baseline variables: Median (IQR)							
Female partner's age, median years (IQR)	27 (23, 31)	26 (23, 29)	27 (23, 31)	0.96 (0.92-1.01)	0.11	0.97 (0.92-1.02)	0.24
Male partner's age, median years (IQR)	32 (28, 36)	30 (27, 36)	32 (28, 36)	1.00 (0.99-1.00)	0.89	1.00 (0.99-1.00)	0.91
Number of children	2 (1-3)	1 (1,2)	2 (1,3)	0.85 (0.72-0.99)	0.04	0.95 (0.72-1.23)	0.68
Time since HIV diagnosis (years)*	3 (1, 6)	4 (1, 6)	3 (1, 6)	1.03 (0.95-1.12)	0.48	1.00 (1.00-1.00)	0.32
Sexual intercourse episodes, last month	3 (1, 5)	2 (0, 4)	3 (2, 6)	0.96 (0.93-0.99)	0.02	0.96 (0.92-0.99)	0.04
Relationship Satisfaction Questions (subset)	Overall, N = 174	Separated during study, N = 43	Stayed together, N = 131	Unadjusted RR (95% CI)	p	Adjusted RR (95% CI)	p
How often do you discuss, or have you considered divorce, separation, or terminating your partnership?							
Never	107 (62%)	27 (63%)	80 (62%)	Ref		Ref	
Occasionally/rarely	43 (25%)	7 (16%)	36 (28%)	0.58 (0.23-1.45)	0.24	0.56 (0.22-1.46)	0.24
Most of the time	23 (13%)	9 (21%)	14 (11%)	1.90 (0.74-4.90)	0.18	1.49 (0.54-4.14)	0.44
Do you ever regret that you entered a relationship with your partner?							
Never	90 (52%)	18 (42%)	72 (55%)	Ref		Ref	
Occasionally/rarely	58 (34%)	9 (21%)	49 (38%)	0.73 (0.31-1.77)	0.49	0.60 (0.26-1.67)	0.38
Most of the time	25 (14%)	16 (37%)	9 (6.9%)	7.11 (2.71-18.69)	<0.001	8.54 (2.90-25.2)	<0.001
How often do you and your partner quarrel?							
Never	54 (31%)	14 (33%)	40 (31%)	Ref		Ref	
Occasionally/rarely	102 (59%)	19 (44%)	83 (64%)	0.65 (0.30-1.44)	0.29	0.75 (0.33-1.71)	0.50
Most of the time	17 (9.8%)	10 (23%)	7 (5.4%)	4.08 (1.30-12.78)	0.01	3.71 (1.12-12.3)	0.04

^a Adjusted for maternal age

^b Adjusted for maternal age and education

^c Adjusted for maternal age, education, and marital status

Table II. Descriptive characteristics of enrolled men, and regression models comparing men who did and did not separate with their partners

Baseline Characteristic	Overall, N = 237	Separated during study, N = 21	Stayed together, N = 216	Unadjusted RR (95% CI)	p	Adjusted RR (95% CI)	p
Education							
Secondary or higher (>13 years)	62 (26%)	2 (9.5%)	60 (28%)	Ref		Ref	
Primary completed, secondary incomplete (7-13 years)	92 (39%)	7 (33%)	85 (39%)	1.47 (0.50-12.31)	0.27	-	-
Less than primary (<7 years)	83 (35%)	12 (57%)	71 (33%)	5.07 (1.10-23.55)	0.04	-	-
Employment							
Salaried	47 (20%)	2 (9.5%)	45 (21%)	Ref		Ref ^a	
Hourly work	63 (%)	8 (%)	55 (%)	3.27 (0.66-16.19)	0.15	3.05 (0.61-15.40)	0.18
Self-employed	123 (52%)	11 (52%)	112 (52%)	2.21 (0.47-10.37)	0.32	2.41 (0.50-11.57)	0.27
Unemployed	4 (2%)	0 (0%)	4 (1.9%)	0.00 (0.00-Inf)	0.99	0.00 (0.00-Inf)	0.99
Relationship factors							
Not currently married (ref: married)	5 (2%)	3 (14%)	2 (1%)	11.89 (1.58-89.5)	0.02	12.08 (1.43-100)^b	0.02
Not living together (ref: living together)	24 (10%)	7 (33%)	17 (8%)	5.85 (2.08-16.45)	<0.01	4.85 (1.42-16.49)^b	0.01
Had sex <10 times in last month (ref: >10 times)	58 (24%)	8 (38%)	50 (23%)	2.04 (0.80-5.21)	0.14	1.38 (0.49-3.89) ^b	0.54
Polygamous relationship	58 (24%)	9 (43%)	49 (23%)	2.79 (1.10-7.11)	0.03	2.71 (1.04-7.03)^a	0.04
How often do you consider separation?							
Never	151 (64%)	7 (33%)	144 (67%)	Ref		Ref	
Occasionally or rarely	63 (27%)	7 (33%)	56 (26%)	2.57 (0.86-7.66)	0.09	3.60 (1.08-11.98)	0.04
Most of the time	22 (9.3%)	7 (33%)	15 (7%)	9.60 (2.97-31.08)	<0.001	11.61 (3.15-42.8)	<0.001
Happiness in the relationship							
Very happy	159 (67%)	8 (38%)	151 (70%)	Ref		Ref	
Happy	59 (25%)	5 (24%)	54 (25%)	1.75 (0.55-5.57)	0.35	1.78 (0.53-5.99)	0.35
Unhappy	18 (7.6%)	8 (38%)	10 (5%)	15.10 (4.68-48.7)	<0.001	16.04 (4.24-60.7)	<0.001
HIV-related factors							
Male is HIV-positive (ref: HIV-negative)	51 (22%)	7 (33%)	44 (20%)	1.94 (0.74-5.10)	0.18	1.49 (0.53-4.28)	0.45
He does not know female partner's status (Ref: he thinks he knows)	65 (27%)	8 (38%)	57 (26%)	1.72 (0.68-4.36)	0.26	1.73 (0.65-4.62)	0.27
Knows female partner has HIV, among N=172 who report knowing her status	136/172 (79%)	12/13 (92%)	124/159 (78%)	3.39 (0.43-26.95)	0.25	2.72 (0.33-22.2)	0.35
Ever reports female partner is positive during study (ref: never reports)	173 (73%)	17 (81%)	156 (72%)	1.63 (0.53-5.06)	0.39	1.47 (0.46-4.69)	0.51
Among HIV-negative men:							
Fear of getting HIV							

Not worried	66 (36%)	5 (36%)	61 (36%)	Ref		Ref	
Some worry	72 (39%)	4 (29%)	68 (40%)	0.72 (0.18-2.79)	0.63	0.60 (0.14-2.43)	0.48
A lot of worry	47 (25%)	5 (36%)	42 (25%)	1.45 (0.40-5.33)	0.57	1.36 (0.35-5.25)	0.67
Motivation to use PrEP							
Very motivated	99 (54%)	6 (42.8%)	93 (54.4%)	Ref		Ref	
Somewhat motivated	37 (20%)	4 (29%)	33 (19%)	1.88 (0.50-7.08)	0.35	1.88 (0.46-7.65)	0.38
Not at all motivated	49 (26%)	4 (29%)	45 (26%)	1.38 (0.37-5.13)	0.63	1.51 (0.38-6.01)	0.56

^a Adjusted for male education

^b Adjusted for maternal education and marital status

Table III. Descriptive characteristics of the PWLHIV and male partners captured in the nested qualitative study

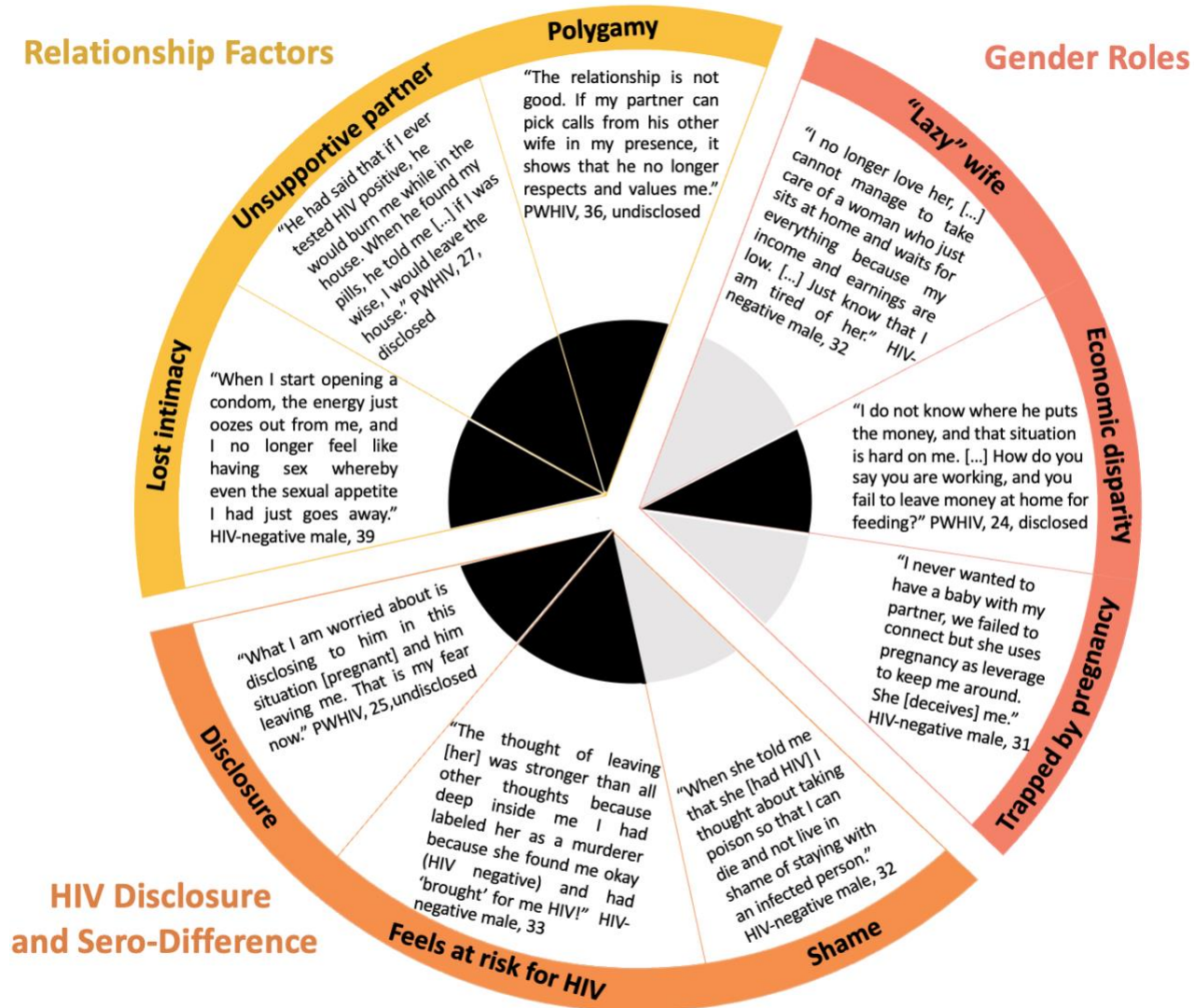
	Women, N=45	Men, N=45
Self-reported HIV-positive	45 (100%)	8 (18%)
HIV status disclosure to partner by time of interview	24 (53%) women disclosed HIV-positive status to partner	29 (64%) male partners knew their female partner has HIV
Median age, years (IQR)	27 (IQR: 25-30)	31 (IQR: 28-35)
Median relationship length, years (IQR)	3 (IQR: 2-7)	3 (IQR: 2-8)
Reported ever separating during study follow-up	6 (13%)	2 (4%)

Table IV. Adjusted regression models assessing the impact of separation on women's viral suppression (<200 copies/ml) at 12 months post-partum, adjusted for age, marital status, education, and recent HIV diagnosis, among 439 women with viral load data at baseline and endline

Outcome	Overall, N = 439	Separated during study, N = 106	Stayed together, N = 333	Adjusted RR (95% CI)	p
Reports poor ART adherence at endline	13 (3%)	6 (6%)	7 (2%)	3.33 (0.99-11.28)	0.05
Virally unsuppressed at endline	47 (11%)	16 (15%)	31 (9%)	1.42 (0.69-2.92)	0.33
Change of viral suppression from baseline to endline					
Remained Suppressed	302 (69%)	70 (66%)	232 (70%)	-	-
Remained Unsuppressed	27 (6.2%)	9 (8.5%)	18 (5.4%)	-	-
Suppressed to Unsuppressed	20 (4.6%)	7 (6.6%)	13 (3.9%)	-	-
Unsuppressed to Suppressed	90 (21%)	20 (19%)	70 (21%)	-	-

Figure I. Circular joint diagram of common factors associated with separation

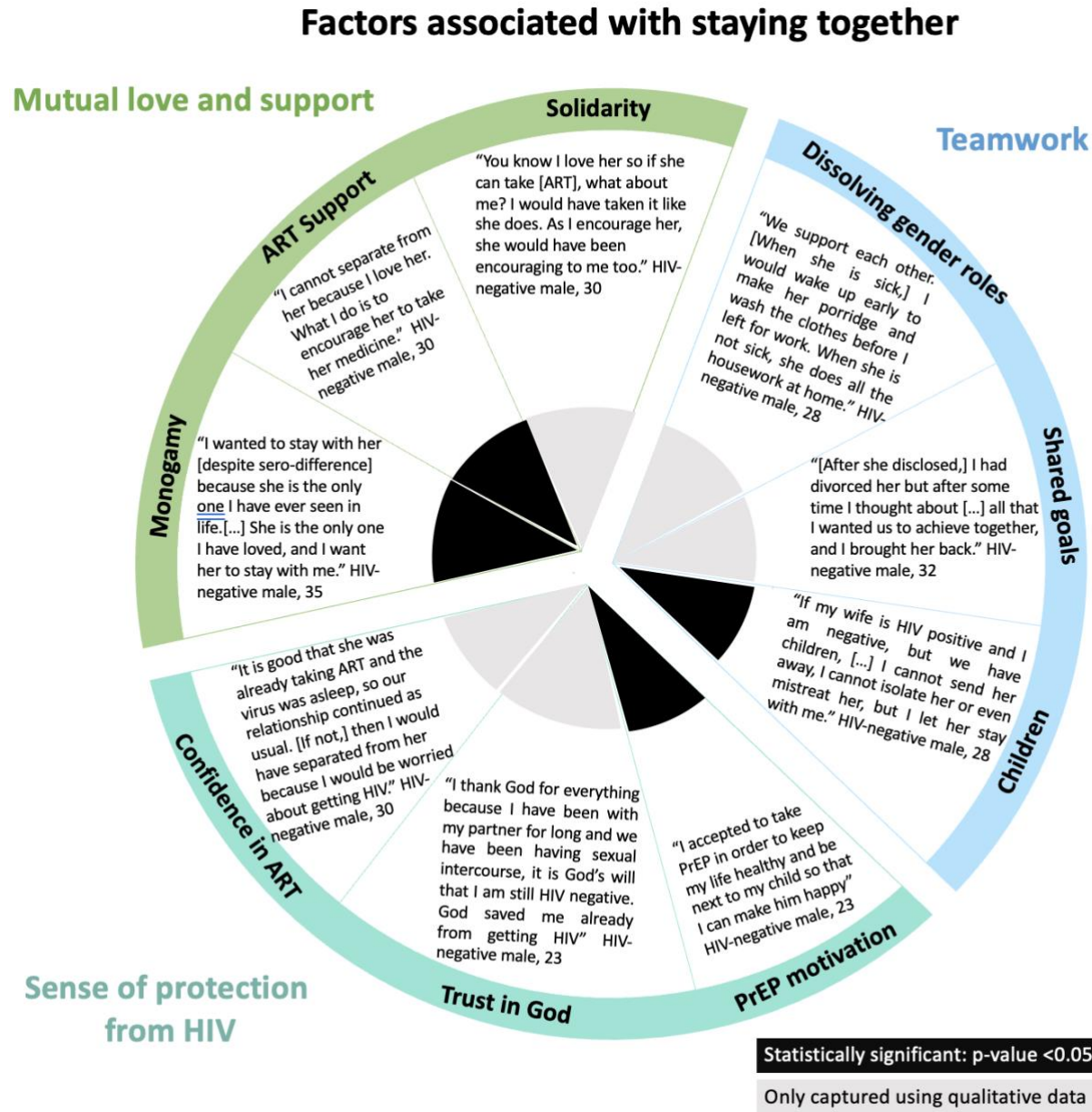
Factors associated with separation among HIV-affected couples



Statistically significant: p-value <0.05

Only captured using qualitative data

Figure II. Circular joint diagram of common factors associated with staying together



CHAPTER II: CHILD NEURODEVELOPMENT AMONG CHILDREN WHO ARE HIV-EXPOSED UNINFECTED IN KENYA

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Publication Status

This was an invited manuscript currently under peer review for JIAS' *Upcoming Special Issue on Children who are Perinatally Exposed to HIV*, to be published in November 2023.

ABSTRACT

Background: Studies suggest increased risk of neurodevelopmental delay among children who are HIV-exposed uninfected (CHEU) compared to their HIV-unexposed uninfected peers (CHUU), but predictors of neurodevelopment among CHEU remain poorly understood.

Methods: Mothers with and without HIV and their children were enrolled during 6-week routine postnatal care visits across six sites in Kenya. Infant neurodevelopment was assessed using the Malawi Developmental Assessment Tool, including social, language, fine motor, and gross motor domains. This exploratory analysis used multivariate linear mixed effects models to identify associations between neurodevelopment scores, HIV and ART exposure, and maternal factors, adjusting for confounders selected *a priori* and clustering by site.

Results: At 1-year evaluation, CHUU (N=715) and CHEU (N=416) had comparable median age (52 weeks) and sex distribution (52% vs. 51% female). Mothers with HIV were older (31 vs. 28 years), had lower education (49% vs. 27% primary), were more likely to be unmarried (14% vs. 12%) or in a polygamous marriage (14% vs. 4%), and report moderate-to-severe food insecurity (19% vs. 9%) ($p < 0.01$ for all). CHEU and CHUU had comparable neurodevelopment scores across all four domains ($p > 0.1$ for all). Among all children, maternal report of intimate partner violence (IPV) was significantly associated with lower gross motor scores (adjusted coefficient: -1.34, 95% CI: -2.18, -0.48). Maternal marital status, and having a deceased or absent father, were significantly associated with lower child neurodevelopment, across multiple domains. Among CHEU, lower gross motor scores were associated with *in utero* efavirenz exposure during pregnancy compared to dolutegravir (DTG) exposure (adjusted coeff: -0.55, 95% CI: -1.06, -0.05) and longer maternal ART duration. Maternal mental health measures were not associated with child neurodevelopment.

Conclusion: Biologic and social factors were associated with child neurodevelopment, and despite several sociodemographic differences between CHEU and CHUU, 1-year neurodevelopment was similar. Addressing IPV may provide benefits for both mother and child, regardless of maternal HIV status. DTG use was associated with higher neurodevelopmental scores in CHEU, compared to EFV-based regimens, potentially contributing to a lack of neurodevelopmental difference observed between CHEU and CHUU.

INTRODUCTION

Successful prevention of vertical transmission programs over the last decade have 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)^{19,20}. 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 HIV²⁰⁻²⁸. 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 five years of age at risk of not meeting their developmental potential^{101,102}. Early neurodevelopmental delays are associated with poorer physical and mental health and learning potential¹⁰¹. A child's neurodevelopment is remarkably sensitive to parental caregiving and home environment factors, especially during the first 1,000 days of life. It is possible to reverse early delays in children, and the earlier the intervention, the greater the impact^{103,104}.

Most, but not all, studies have found increased risk of neurodevelopmental delays in CHEU compared to their CHUU peers. Previous studies are limited by small sample sizes, only relying on one time-point for outcome measurement, and heterogeneity in ART exposures overtime. Preterm birth, *in utero* ART exposure, maternal viremia, and early child inflammatory markers have been associated with significantly poorer neurodevelopment among CHEU²⁹⁻³¹. Studies have noted differences in language, social and motor skills, brain composition and structure, and altered cell-mediated immunity between CHEU and CHUU^{27,32,33}. While biologic etiologies of neurodevelopmental outcomes among CHEU have been assessed, there are fewer data on modifiable, social and behavioral 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^{14-17,34,37,102,105-108}.

Kenya alone is home to nearly 1 million CHEU for whom research is urgently needed to identify caregiver and home factors to reduce the risk of suboptimal child neurodevelopment¹⁹. In 2016, the World Health Organization (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 age¹⁰⁹. Prior to DTG scale up, nonnucleoside reverse transcriptase inhibitor (NNTRI) 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 regimens¹¹⁰. DTG-based regimens and EFV-based regimens have comparable safety in pregnancy,¹¹¹ 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.

METHODS

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 (1,000 CHEU and 1,000 CHUU) at 4-10 weeks of age during routine postnatal care at 6 MCH clinics across the Nairobi and Western Kenya regions between March 2021-June 2022. Mother-infant pairs are being followed every six 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 by December 2022.

Data Collection

Outcome ascertainment: To measure child neurodevelopment, we administered the Malawi Developmental Assessment Tool (MDAT)¹¹², a validated test designed specifically for the SSA cultural context. The MDAT scores social, language, fine motor, and gross motor domains, 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, until a child reached six consecutive passes and six consecutive fails in each domain. MDAT scores were assessed as raw continuous scores per domain. Assessors underwent a rigorous training curriculum and each conducted ≥ 10 supervised practice assessments prior to certification and study start. We utilized 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 reviewed every 10th assessment to ensure consistency.

Exposures ascertainment: A primary exposure of interest was maternal HIV status (CHEU vs. CHUU). Any children who later tested positive for HIV were excluded from this analysis. Exposure variables collected at baseline (6 weeks postpartum) included maternal sociodemographic information, family

characteristics, medical history, household factors, anthropometric measures (e.g., body mass index (BMI)) and mental health assessments: the 9-item Patient Health Questionnaire (PHQ-9, ≥ 10 cut-off)¹¹³ for clinical depression, 10-item Kessler Psychological Distress Scale (K10, ≥ 20 cut-off)^{114,115} for anxiety, and Hurt-Insult-Threaten-Scream (HITS, ≥ 10 cut-off)¹¹⁶ for intimate partner violence. The degree of household food insecurity was assessed using the Household Hunger Scale¹¹⁷. Additionally, mothers living with HIV were asked questions regarding HIV, experience with status disclosure to their partner, and ART initiation, duration, and regimen.

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* and clustering by site. 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 considered *a priori* for adjustment in multivariable analyses included maternal age (years), education level, marital status, and infant sex and age (weeks). Based on literature, we expected these factors to be associated with exposures, such as maternal HIV status, and child neurodevelopment scores.^{27,118} 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 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-conception/during pregnancy or postpartum), HIV disclosure to partner (ever/never), and ART regimen (DTG, EFV, or protease inhibitor (PI)-based).

Ethical Board Approvals

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

RESULTS

Study Population

All children (N=1,131) (Table 1)

This analysis used data collected from 416 CHEU and 715 CHUU and their mothers. Compared to CHUU, CHEU had comparable median age at 1-year neurodevelopmental assessment (52 weeks) and sex distribution (52% vs. 51% female). 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. 28 years), with only primary school education (49% vs. 27%), either single, separated or widowed (12% vs. 7%) or in a polygamous marriage (14% vs. 4%), report moderate-to-severe food insecurity (19% vs. 9%), and have BMI <18.5 (5% vs. 2%; $p < 0.01$ for all). Maternal mental health screening assessments of clinical depression and/or anxiety, and reported intimate partner violence, were comparable between mothers with and without HIV.

CHEU only (N=416) (Table 2)

Among mothers living with HIV, all were on ART; 88% started ART pre-conception, and 12% post-conception. At baseline, 87% of mothers had already disclosed their HIV status to their primary partner and had already been taking ART for a median of 53 months (IQR: 20-85). Among mothers with ART regimen data during pregnancy ($n=375$), the most recently used maternal ART regimen during pregnancy was DTG-based (69%), followed by EFV-based (23%) and PI-based regimens (7%). Mothers of EFV-exposed CHEU had been on ART for longer than mothers of DTG-exposed CHEU (median 61 vs. 45 months). Overall, 40% of mothers switched their ART regimen during pregnancy, and 76% of them had switched to DTG-based regimens. Almost all (98%) of CHEU had received antiretroviral prophylaxis by 6 weeks of age; 53% received a nevirapine (NVP)-only regimen and 47% received azidothymidine (AZT)-based regimens (largely AZT/NVP combinations).

Potential cofactors of child neurodevelopment

MDAT score comparison for CHEU vs. CHUU (Tables 3 and 4a)

Overall, the CHEU and CHUU groups had comparable 1-year neurodevelopment scores across all four domains, in both univariable and multivariable mixed linear effects models with site clustering and adjustment for infant age and sex, and maternal education and marital status ($p > 0.1$ in all four domains).

Cofactors of MDAT scores among all children, adjusting for CHEU status (Table 4a and Figure 1)

Compared to female children, male children scored significantly lower in both the social (adjusted coefficient: -0.42, 95% CI: -0.71, -0.12, $p < 0.01$) and language domains (adjusted coefficient: -0.24, 95% CI: -0.41, -0.07, $p < 0.01$). The prevalence of baseline maternal IPV was 3% in each group; among all children adjusting for maternal HIV status and confounders *selected a priori*, IPV was significantly

associated with lower gross motor scores (adjusted coefficient: -1.18, 95% CI: -1.98, -0.36, $p < 0.01$). Maternal marital status was associated with child neurodevelopment; compared to children with mothers in monogamous marriages, children with single or widowed mothers had significantly lower social scores (adjusted coefficient: -0.59, 95% CI: -1.13, -0.07, $p = 0.03$) and children with mothers in steady relationships (but not formally married) had significantly lower fine motor scores (adjusted coefficient: -0.59, 95% CI: -1.15, -0.02, $p = 0.04$). Children whose fathers were either deceased or absent had significantly lower fine motor scores (adjusted coefficient: -0.48, 95% CI: -0.48, -0.03, $p = 0.04$). There were no statistically significant associations between child neurodevelopment and maternal depression, anxiety, or distress.

Cofactors of MDAT scores among CHEU only (Table 4b and Figure 2)

In multivariate models, consistent with analyses among all children, male CHEU scored significantly lower than female CHEU in both the social (adjusted coefficient: -0.62, 95% CI: -1.12, -0.12, $p = 0.01$) and language domains (adjusted coefficient: -0.28, 95% CI: -0.55, -0.01, $p = 0.04$). Compared to CHEU with mothers in monogamous marriages, CHEU with mothers in steady relationships (but not formally married) had significantly lower language scores (adjusted coefficient: -0.95, 95% CI: -1.81, -0.07, $p = 0.03$). CHEU whose fathers were either deceased or absent had significantly lower scores in language (adjusted coefficient: -0.57, 95% CI: -1.03, -0.11, $p = 0.02$), fine motor (adjusted coefficient: -0.80, 95% CI: -1.48, -0.12, $p = 0.02$) and gross motor domains (adjusted coefficient: -1.00, 95% CI: -1.70, -0.25, $p < 0.01$).

In adjusted models, neurodevelopment was significantly associated with maternal ART duration and regimen. Gross motor scores were significantly lower with *in utero* exposure to EFV-regimens than DTG-based regimens (adjusted coefficient: -0.55, 95% CI: -1.06, -0.05, $p = 0.03$). Irrespective of maternal ART regimen, on average, CHEU scored -0.01 point lower in the gross motor domain for every additional month their mother was taking ART (adjusted coefficient: -0.01, 95% CI: -0.01, -0.01, $p = 0.03$). Among CHEU exposed most recently to EFV during pregnancy, maternal ART duration was not associated with any domain scores; however, among CHEU exposed most recently to DTG during pregnancy, longer maternal ART duration was significantly associated with lower gross motor scores (adjusted coefficient: -0.01, 95% CI: -0.02, -0.00, $p < 0.01$). MDAT scores were not associated with pre- vs. post-conception ART initiation. CHEU with mothers with heightened depression at baseline scored slightly higher in their 1-year language domain compared to those with mothers with lower scores (adjusted coefficient: 0.86, 95% CI: 0.04, 1.68, $p = 0.04$). Neurodevelopment was not associated with other maternal mental health factors.

DISCUSSION

In this cohort of 1-year old children, we found that CHEU and CHUU had comparable neurodevelopment scores across all four tested domains, both in unadjusted and adjusted analyses. Among all children, lower child neurodevelopment scores were associated with male sex, maternal marital status, deceased or absent father, and maternal report of IPV. Among CHEU only, these associations persisted, and lower child neurodevelopment scores were also associated with longer maternal ART duration and *in utero* exposure to EFV-based ART regimens, compared to DTG-based regimens.

Reassuringly, CHEU in this study had similar neurodevelopmental scores to their HIV-unexposed peers. Studies comparing neurodevelopment between CHEU and CHUU, including with the MDAT tool, have found higher risk of language and motor skill delays in CHEU; these differences were linked to altered brain composition and structure, immune function, adverse birth outcomes, and growth faltering^{27,30,32,33,118-121}. In an extensive meta-analysis of 21 studies comparing neurodevelopment between CHEU and CHUU under five years, 57% of studies found subtle delays among CHEU in at least one domain, and primarily in the language and gross motor domains¹¹⁸. Included studies had relatively small sample sizes, and relied on studies published prior to May 2020; it is possible that more recent universal test and treat guidelines and newer, improved ART regimens using DTG-based combinations, as well as guidelines promoting longer breastfeeding duration may improve child outcomes. Almost 70% of mothers living with HIV in this study with available ART data were on DTG-based regimens during their pregnancy, which is substantially higher than in previously published studies assessing neurodevelopment among CHEU, and may be part of the reason we see comparable scores between CHEU and CHUU in our cohort.

Effects of ART regimens on CHEU neurodevelopment have been studied with mixed results¹¹⁸. 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 regimens¹¹¹. EFV-based regimens have been associated with higher risk of microcephaly and other neurologic disorders among CHEU¹²². We found that *in utero* EFV-exposed CHEU scored significantly lower in gross motor than DTG-exposed CHEU. Similarly, 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)¹¹⁰. Moreover, EFV-exposed children had longer exposure to ART (since conception vs. third trimester) than children exposed to other regimens, and

longer EFV exposure was associated with more pronounced deficits¹¹⁰. The study was conducted prior to large scale up of DTG-based regimens and could not assess whether DTG-exposed CHEU performed better than EFV-exposed CHEU. Similarly, we also found that mothers of EFV-exposed CHEU had been on ART for longer than mothers on newer DTG-based regimens (median 61 vs. 45 months), and longer maternal ART duration was associated with lower gross motor scores. It is unclear whether higher neurodevelopment scores among DTG-exposed CHEU is due to biologic or sociobehavioral factors, or a combination. Despite WHO recommendations, DTG uptake has remained suboptimal in SSA among reproductive-aged women, partly due to initial concerns around neural tube defects¹²³. 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 period of changing regimen implementation, providing a unique opportunity to examine the impact of different regimens. Our data provides reassuring evidence of another potential benefit of DTG-regimens.

Maternal marital status, absence of biologic father, and IPV were significantly associated with lower child neurodevelopment scores. Parental relationship conflict and household exposure to violence (interparental or onto child) can considerably threaten a child's neurodevelopment^{37-39,77-79,124,125}. Over a quarter of women of reproductive age in Eastern Africa were estimated to have experienced IPV in the past year^{15,46,126}. In this cohort, maternal report of IPV was strongly associated with poorer gross motor scores among all children, controlling for maternal HIV status. Abuse and separation can often lead to disproportionate burdens on women, leading to financial hardship, childcare responsibility, and social stigma^{47,48}. 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^{98,99}. HIV-affected couples separate frequently during pregnancy/postpartum when HIV testing is common, and HIV serodifferent couples in which the female is living with HIV separate significantly more often than couples in which the is living with HIV¹³. CHEU whose mothers had depression at baseline performed slightly better in the language domain than those whose mothers did not have depression; it is unclear whether this finding is due to risk of false discovery, so further research may be needed in this area. Paternal involvement can improve birth outcomes, parental satisfaction, maternal engagement with care, and child growth and development^{4,5,8-11}. 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 neurodevelopment⁹¹⁻⁹⁴. This or similar interventions could be adopted within maternal child health or PMTCT programs in Kenya.

CHEU were significantly more likely than CHUU to have a mother who is single, widowed, or in a polygamous relationship. In East African contexts in which men having multiple wives is a legal and socially accepted practice, polygamy is associated with HIV; among a cohort of 500 Ugandan pregnant women living with HIV, 30% were in polygamous marriages, which was substantially higher than the 8% average among marriages nationally^{72-74,108}. Similarly, in our cohort, the prevalence of polygamy was significantly higher among mothers living with HIV than mothers without (14% vs. 4%). Polygamy among HIV-affected couples has been associated with HIV status non-disclosure, lack of social support from partner, and relationship conflict and dissolution^{44,108}. Tailored interventions to support women and children in the context of polygamy may be important to develop programmatically.

Among all children, regardless of *in utero* HIV exposure, male sex was associated with lower MDAT scores in the social and language domains. We did not find any significant sociodemographic differences between male and female children. Two studies, one from Zimbabwe and another from Uganda, both found HIV exposure negatively impacted children's MDAT scores, but neither study found any associations with child sex^{120,121}. Historically, child sex bias has skewed clinical diagnoses for neurodevelopmental disorders and intellectual delays towards boys, most notably in autism spectrum disorder¹²⁷. Research into the mechanistic pathways of such neurodevelopmental sex differences have found complex interactions between different behavioral expression, biologic and environmental factors¹²⁸. It is unclear why boys in our study, on average, performed poorer than girls, and should be investigated further to see if differences by sex persist over time.

Our study has several strengths, including its large sample size and longitudinal design. The cohort (1000 CHEU/1000 CHUU) is still accruing with undergoing 6-monthly neurodevelopment assessments until children reach 3 years, which will allow for future longitudinal analyses. We used the MDAT assessment, which was developed specifically for use in SSA, and relies on both direct child observation and caregiver report. All assessors underwent a rigorous training and quality control process to improve accuracy and reliability of the assessment data. Limitations of the study include that our analyses used data from 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 the ART exposures were only conducted among those with ART data. ART-regimen classification was dichotomous and based on the

most recently used regimen at the time of enrollment, which does not account for heterogeneity due to switches or interruptions. This analysis may be subject to selection and sampling bias based on inclusion criteria; our study does not capture mothers <18 years old, mothers not engaged in postnatal care or PMTCT programs, and children whose mothers died prior to the child reaching six 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.

CONCLUSION

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 and IPV were associated with poorer neurodevelopmental scores in all children, regardless of maternal HIV status. Rigorous longitudinal and mixed methods research are needed to identify modifiable factors among families impacted by HIV and caregiver relationship conflict, and to identify interventions to best support children showing early deficits.

Competing Interests: The authors have no conflicts of interest to disclose.

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

Acknowledgements: We thank the mothers and children who participated in this study.

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). 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 author GJS, upon reasonable request.

CHAPTER II: TABLES & FIGURES

Table 1. Sociodemographic Characteristics comparing CHEU and CHUU

Characteristic	Overall, N = 1,131 [†]	CHEU, N = 416 [†]	CHUU, N = 715 [†]	Unadjusted p-value
Region				
Nairobi	461 (41%)	146 (35%)	315 (44%)	Ref
W Kenya	669 (59%)	270 (65%)	399 (56%)	<0.01
Child sex is female	584 (52%)	216 (52%)	368 (51%)	0.88
Child age (weeks)	52 (3)	52 (3)	52 (3)	0.10
Birthweight <2500g	241 (21%)	72 (17%)	169 (24%)	0.01
Born at least 2 weeks prematurely	66 (5.9%)	29 (7.1%)	37 (5.2%)	0.21
Child has deceased or absent biological father	78 (6.9%)	40 (9.6%)	38 (5.3%)	<0.01
Exclusively breastfed at 6 weeks	1,097 (97%)	411 (100%)	686 (96%)	<0.01
Number of times breastfed in last 24 hours	15 (27)	16 (44)	14 (4)	0.22
Mother age (years)	28.9 (5.5)	31.0 (5.7)	27.6 (5.0)	<0.01
Mother education, primary or less	395 (35%)	203 (49%)	192 (27%)	<0.01
Mother is employed (professionally or casually)	231 (20%)	93 (22%)	138 (19%)	0.22
Mother marital status				
Married (monogamous)	895 (79%)	298 (72%)	597 (84%)	ref

Characteristic	Overall, N = 1,131 ¹	CHEU, N = 416 ¹	CHUU, N = 715 ¹	Unadjusted p-value
Married (polygamous)	88 (7.8%)	60 (14%)	28 (3.9%)	<0.01
Steady partner	47 (4.2%)	10 (2.4%)	37 (5.2%)	0.09
Single, separated, or widowed	99 (8.8%)	48 (12%)	51 (7.2%)	<0.01
Mother height (cm)	162 (9)	162 (10)	162 (8)	0.25
Mother BMI <18.5	32 (2.9%)	19 (4.6%)	13 (1.9%)	<0.01
Mother MUAC (cm)	29.4 (29.2)	30.5 (47.9)	28.8 (3.9)	0.43
Moderate or severe hunger in the household	147 (13%)	80 (19%)	67 (9.4%)	<0.01
Heightened depression	39 (3.5%)	11 (2.7%)	28 (3.9%)	0.26
Heightened anxiety	88 (7.8%)	38 (9.2%)	50 (7.0%)	0.19
Heightened distress	107 (9.5%)	43 (10%)	64 (9.0%)	0.44
Intimate partner violence	28 (2.5%)	9 (2.2%)	19 (2.7%)	0.61

¹ n (%); Mean (SD)

Table 2. Characteristics of CHEU population

Characteristic	N = 416 ¹
Child ARV prophylaxis	408 (98%)
Child ARV regimen	
AZT-based	192 (47%)
NVP alone	216 (53%)

Characteristic	N = 416 ¹
ART start timing	
Pre-conception	350 (88%)
Post-conception	48 (12%)
Most recent maternal ART regimen during pregnancy (n=375)	
DTG based	260 (69%)
EFV based	88 (23%)
PI based or other	27 (7.2%)
Maternal duration on ART (months)	53 (20-85)
Switched ART during pregnancy	154 (40%)
Disclosed HIV status to partner	362 (87%)

¹ n (%); Median (IQR)

Table 3. Comparison of raw MDAT scores at 1 year between CHEU and CHUU

Characteristic	Overall, N = 1,131 ¹	CHEU, N = 416 ¹	CHUU, N = 715 ¹	Unadjusted P-value
Social	13.8 (3.2)	13.9 (3.1)	13.7 (3.2)	0.83
Language	9.28 (1.75)	9.29 (1.80)	9.28 (1.72)	0.38
Fine Motor	15.24 (2.11)	15.17 (2.19)	15.28 (2.07)	0.11
Gross Motor	15.69 (2.18)	15.64 (2.20)	15.72 (2.17)	0.54

¹ Mean (SD)

Table 4a. Cofactors of MDAT scores at 1-year among overall cohort (CHEU and CHUU)

	Social, Adjusted Coeff (95% CI)	<i>P</i>	Language, Adjusted Coeff (95% CI)	<i>P</i>	Fine Motor, Adjusted Coeff (95% CI)	<i>P</i>	Gross Motor, Adjusted Coeff (95% CI)	<i>P</i>
ENTIRE COHORT – CHEU vs. CHUU								
CHEU (ref: CHUU) – Unadjusted	-0.03 (-0.35, 0.28)	0.83	0.08 (-0.10, 0.26)	0.38	-0.19 (-0.43, 0.05)	0.11	-0.08 (-0.35, 0.19)	0.54
CHEU (ref: CHUU) – Adjusted ^a	0.14 (-0.18, 0.47)	0.94	0.15 (-0.03, 0.38)	0.15	-0.08 (-0.33, 0.16)	0.51	-0.06 (-0.33, 0.22)	0.68
ENTIRE COHORT – adjusting for CHEU status								
Child sex ^b								
Child is male (ref: female)	-0.42 (-0.71, -0.12)	<0.01	-0.24 (-0.41, -0.07)	<0.01	0.05 (-0.17, 0.28)	0.66	0.10 (-0.16, 0.35)	0.45
Maternal mental health at 6 weeks postpartum ^b								
Heightened depression (PHQ-9 score \geq 10)	-0.43 (-1.24, 0.37)	0.29	0.29 (-0.17, 0.75)	0.22	-0.06 (-0.68, 0.56)	0.85	0.51 (-0.17, 2.24)	0.15
Heightened anxiety (K10 score \geq 20)	0.31 (-0.25, 0.87)	0.27	0.11 (-0.20, 0.44)	0.46	0.14 (-0.28, 0.57)	0.51	-0.23 (-0.70, 0.25)	0.34
Heightened distress (depression and/or anxiety)	0.06 (-0.45, 0.57)	0.83	0.11 (-0.18, 0.40)	0.47	0.03 (-0.36, 0.42)	0.89	-0.20 (-0.63, 0.25)	0.38
Family factors at 6 weeks postpartum ^b								
Deceased or absent biologic father	-0.27 (-0.86, 0.32)	0.37	-0.26 (-0.59, 0.08)	0.14	-0.48 (-0.93, -0.03)	0.04	-0.17 (-0.67, 0.35)	0.52
Intimate partner violence (HITS score \geq 10)	0.13 (-0.82, 1.08)	0.79	0.41 (-0.13, 0.94)	0.14	-0.59 (-1.32, 0.13)	0.11	-1.18 (-1.98, -0.36)	<0.01
Maternal marital status								
Married – monogamous	Ref		Ref		Ref		Ref	
Married – polygamous	-0.22 (-0.79, 0.36)	0.46	0.01 (-0.32, 0.34)	0.95	-0.05 (-0.50, 0.38)	0.81	0.39 (-0.11, 0.88)	0.12
Steady partner, not married	-0.14 (-0.88, 0.59)	0.71	-0.20 (-0.62, 0.22)	0.35	-0.59 (-1.15, -0.02)	0.04	0.32 (-0.31, 0.95)	0.32
Single or widowed	-0.59 (-1.13, -0.07)	0.03	-0.22 (-0.52, 0.08)	0.15	-0.24 (-0.64, 0.17)	0.25	-0.27 (-0.72, 0.19)	0.24
Moderate to severe household food insecurity	-0.12 (-0.57, 0.34)	0.61	-0.01 (-0.27, 0.25)	0.93	-0.11 (-0.46, 0.24)	0.53	-0.22 (-0.60, 0.18)	0.28

^a Multivariable mixed effects linear models adjusted for infant age and sex, and maternal education and marital status.

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

Table 4b. 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
CHEU ONLY								
Child sex^a								
Child is male (ref: female)	-0.62 (-1.12, -0.12)	0.01	-0.28 (-0.55, -0.01)	0.04	0.05 (-0.18, 0.27)	0.68	-0.14 (-0.56, 0.28)	0.52
Maternal mental health at 6 weeks postpartum^a								
Heightened depression (PHQ-9 score ≥ 10)	0.83 (-0.71, 2.36)	0.30	0.86 (0.04, 1.68)	0.04	0.69 (-0.61, 2.00)	0.31	0.36 (-1.02, 1.74)	0.60
Heightened anxiety (K10 score ≥ 20)	0.72 (-0.32, 1.76)	0.18	0.08 (-0.34, 0.84)	0.42	0.46 (-0.42, 1.34)	0.31	0.03 (-0.88, 0.95)	0.95
Heightened distress (depression and/or anxiety)	0.62 (-0.32, 1.56)	0.20	0.34 (-0.19, 0.88)	0.22	0.34 (-0.47, 1.14)	0.42	-0.00 (-0.84, 0.84)	0.99
Family factors at 6 weeks postpartum								
Deceased or absent father ^d	-0.30 (-1.15, 0.56)	0.50	-0.57 (-1.03, -0.11)	0.02	-0.80 (-1.48, -0.12)	0.02	-1.00 (-1.70, -0.25)	<0.01
Intimate partner violence (HITS score ≥ 10) ^c	0.11 (-1.59, 1.82)	0.89	0.77 (-0.14, 1.68)	0.10	0.07 (-1.28, 1.43)	0.92	-1.40 (-2.83, 0.05)	0.06
Maternal marital status: Married – monogamous ^d	Ref		Ref		Ref		Ref	
Married – polygamous	-0.03 (0.75, 0.69)	0.94	0.07 (-0.31, 0.46)	0.71	-0.31 (-0.89, 0.26)	0.29	0.08 (-0.53, 0.68)	0.80
Steady partner, not married	-0.61 (-2.23, 1.01)	0.46	-0.95 (-1.81, -0.07)	0.03	-0.90 (-2.19, 0.38)	0.17	-0.11 (-1.47, 1.25)	0.87
Single or widowed	-0.13 (-0.92, 0.66)	0.76	-0.27 (-0.70, 0.15)	0.21	-0.53 (-1.16, 0.11)	0.10	-0.44 (-1.10, 0.23)	0.19
Moderate to severe household food insecurity	0.13 (-0.51, 0.78)	0.69	0.18 (-0.07, 0.62)	0.12	0.15 (-0.37, 0.66)	0.58	0.21 (-0.43, 0.67)	0.67
Maternal ART characteristics								
Disclosed HIV status by 6 weeks postpartum ^d	-0.12 (-0.97, 0.72)	0.79	-0.09 (-0.54, 0.37)	0.71	-0.03 (-0.72, 0.63)	0.92	0.03 (-0.68, 0.74)	0.94
Mother started ART post-conception (ref: pre-conception) ^d	-0.16 (-1.08, 0.77)	0.74	0.09 (-0.43, 0.62)	0.73	0.35 (-0.44, 1.15)	0.40	0.27 (-0.55, 1.07)	0.52
Duration on ART (months) ^c	-0.00 (-0.01, 0.01)	0.63	-0.00 (-0.01, 0.00)	0.93	-0.00 (-0.01, 0.00)	0.22	-0.01 (-0.01, -0.01)	0.03
ART regimen during pregnancy: DTG-based ^d	Ref		Ref		Ref		Ref	

EFV-based	0.12 (-0.57, 0.79)	0.74	0.08 (-0.28, 0.44)	0.67	0.10 (-0.43, 0.56)	0.72	-0.55 (-1.06, -0.05)	0.03
PI-based	0.70 (-0.33, 1.73)	0.19	0.19 (-0.35, 0.74)	0.48	0.25 (-0.56, 0.62)	0.55	-0.09 (-0.92, 0.73)	0.83

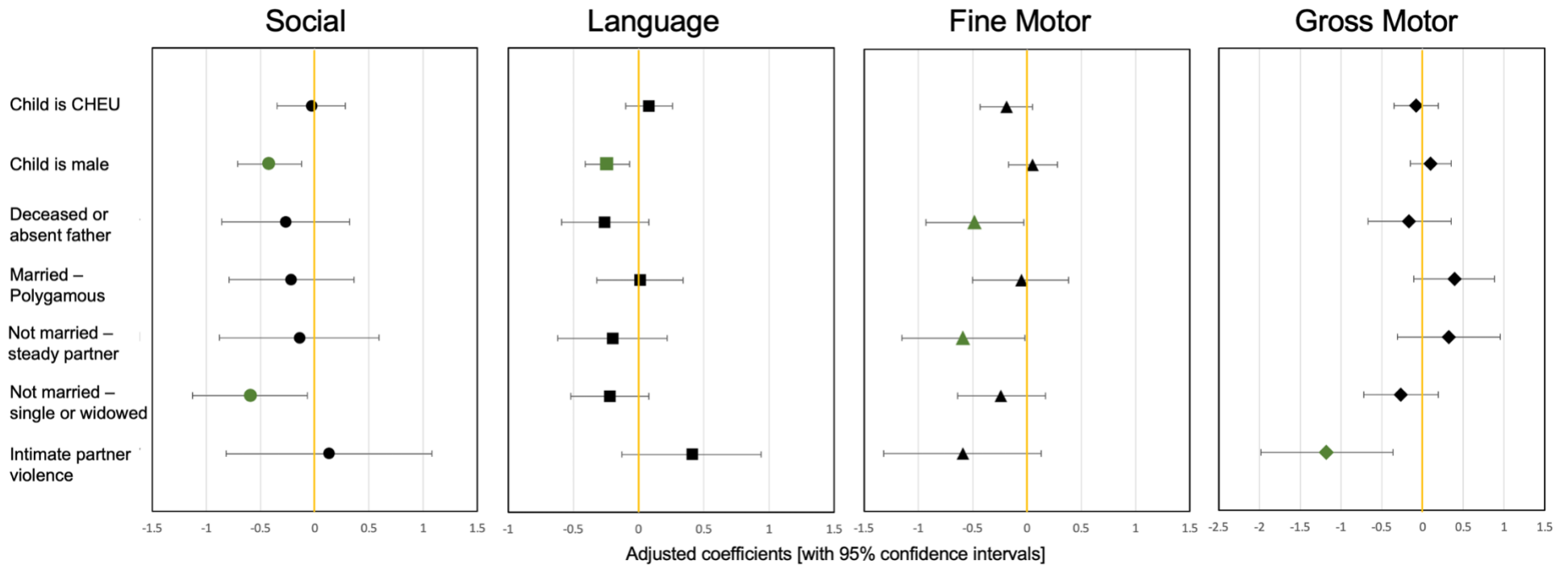
^a Multivariable mixed effects linear models adjusted for infant age and sex, and maternal education and marital status.

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

^c Multivariable mixed effects linear models adjusted for infant age and sex, and maternal education, marital status, and age.

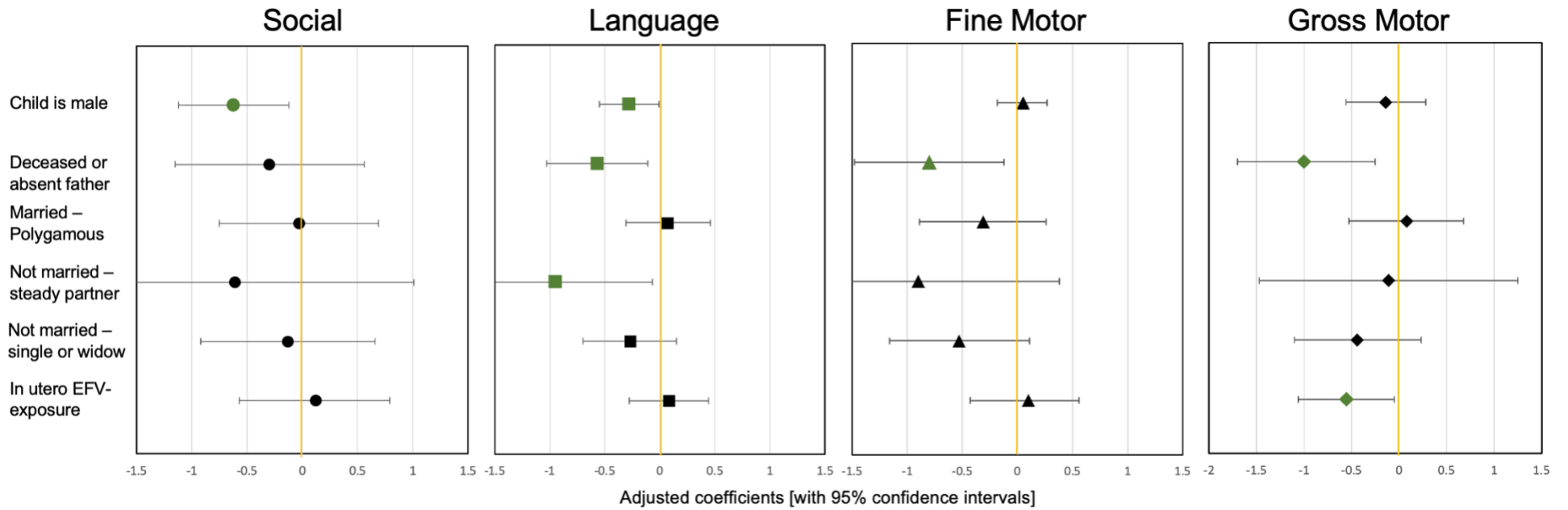
^d Multivariable mixed effects linear models adjusted for infant age and sex, and maternal education.

Figure 1. Forest plots of key cofactors of MDAT scores among all children



Footnote: Signals highlighted in green represent cofactors that are statistically significantly associated with MDAT scores (< 0.00 Adjusted coefficient).

Figure 2. Forest plots of key cofactors of MDAT scores among CHEU only



Footnote: Signals highlighted in green represent cofactors that are statistically significantly associated with MDAT scores (< 0.00 Adjusted coefficient).

CHAPTER III: COMMENTARY ON FACTORS THAT MAY BE IMPACTING CHILD NEURODEVELOPMENT AMONG CHILDREN WHO ARE HIV-EXPOSED UNINFECTED

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PUBLICATION STATUS

This was an invited commentary currently under peer review for JIAS' *Upcoming Special Issue on Children who are Perinatally Exposed to HIV*, to be published in November 2023.

ABSTRACT

Introduction: The population of almost 16 million children under 15 years of age with perinatal HIV exposure who remain HIV uninfected (CHEU) continues to expand rapidly, and the estimated prevalence of CHEU exceeds 20% in several countries in sub-Saharan Africa with high HIV prevalence. This comes with potential population health implications, and some evidence suggests that CHEU experience higher risk of suboptimal neurodevelopmental outcomes compared to their peers born to women without HIV. In this commentary, we discuss the latest research on biologic and behavioral factors associated with neurodevelopmental outcomes among CHEU, from the *in utero* milieu to caregiver-related factors.

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 varied settings, ages, and with varied assessment tools. *In utero* HIV exposure can influence infant immune function, structural brain integrity, systemic inflammation, and growth faltering. Antiretroviral therapy exposure may also influence outcomes. There is need for rigorous harmonized approaches to assess social and behavioral covariates, such as household violence, food insecurity, poor sanitation, and caregiver relationship stability and mental health.

Conclusion: CHEU have biologic and social factors that may influence their brain maturation, immune system, and overall health and wellbeing. Multidisciplinary research is needed to disentangle modifiable aspects of and complex interactions between potential contributing factors. Caregivers and providers need viable strategies to identify children at highest risk for poor outcomes, and early, multisectoral effective interventions are needed to ensure that all CHEU thrive in a manner comparable to their HIV-unexposed peers.

INTRODUCTION

Momentous strides in successful prevention of vertical infant HIV acquisition has resulted in an expanding population of nearly 16 million children who are born HIV-exposed and uninfected (CHEU) ¹⁹. CHEU currently 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 (SSA) ^{19,20}. UNAIDS estimates the prevalence of CHEU ≤ 14 years old exceeds 20% in several countries in SSA, with over one million CHEU born every year (**Figures 1a-b**) ^{19,20}. Simultaneously, SSA is estimated to have the highest prevalence of children under five years at risk of not reaching their developmental potential, underscoring the critical need for rigorous research and implementation science to inform development of interventions and normative guidance to support CHEU to reach their developmental potential ¹²⁹.

CHEU are at higher risk of adverse health outcomes, including 2-3-fold higher risk of infectious-cause hospitalizations and mortality, compared to children who are HIV-unexposed and uninfected (CHUU) ^{19-28,32,130-133}. Not all studies have found higher risk of neurodevelopmental deficits in CHEU than CHUU, but a recent meta-analysis of eight high-quality studies combining neurodevelopment data from 5,000 CHEU and CHUU, mostly from SSA, found CHEU had significantly poorer scores in expressive language and gross motor domains by age 2 years across a variety of settings, ages, and assessment tools ^{22,27,118-120,134-139}. Even subtle impairments to early child neurodevelopment can have critical implications for lifelong physical and mental wellbeing and learning potential. Early interventions targeting children and caregivers can greatly improve outcomes ^{38,39,101,103,104}. This commentary synthesizes existing literature on the key ingredients for cultivating healthy child neurodevelopment and discusses potential biologic and behavioral mechanistic pathways that could synergistically impact neurodevelopment among CHEU (**Figure 1c**).

DISCUSSION

Maternal HIV infection and the intrauterine environment

Various factors directly related to maternal HIV infection have been associated with child neurodevelopmental outcomes. High maternal HIV viremia during pregnancy has been associated with poorer neurodevelopment in expressive language and motor skills among CHEU ³⁰. HIV antigen and ribonucleic acid are detectable in placental and fetal membranes during gestation among pregnant women with HIV ^{140,141}. Maternal HIV infection is associated with abnormal vaginal microbiota, a risk factor for adverse pregnancy outcomes and neurodevelopmental delay in children ¹⁴². Pregnant women

with HIV exhibit higher incidence of endometrial, placental and amniotic infections and inflammation, factors that weaken the intrauterine environment's ability to function optimally ^{130,143}. Perinatal infections such as cytomegalovirus (CMV) are six-times more common among CHEU than CHUU, and are associated with adverse neurodevelopmental, immune, and growth outcomes ^{144,145}. Maternal immune activation, lower maternal CD4 cell counts at delivery, higher incidence of infections, lower transfer of passive antibodies from mother to infant, and altered cell-mediated immune function are all associated with adverse outcomes among CHEU ^{26,32,130,146-149}. Similarly, reduced infant immunity directly increases risk of needing neonatal intensive care, dysfunctional immune responses to immunizations, poor neurodevelopment, hospitalizations and ensuing infectious morbidity ^{26,31,150,151}. Maternal folic acid and iron deficiency during pregnancy can also increase risk of neurodevelopmental delays in children but this potential mechanistic pathway has not been adequately studied among CHEU ¹⁵².

Antiretroviral therapy (ART) exposure

There are inconsistent, mixed, and limited data on the influence of ART exposure on child neurodevelopment ^{27,118,153,154}. Mechanistic pathways by which ARV exposure may have adverse implications on child neurodevelopment include associations between ART exposures and infant immune function. Studies comparing CHEU with and without ART exposure (defined as any *in utero* or neonatal exposure) have found higher ART exposure to be associated with subtle but significantly reduced infant cell counts including low CD8+ cells counts that persist through 8 years ^{155,156}. Some but not all studies have found ARV exposure to older regimens to be significantly associated with higher incidence of drug toxicity (accumulation in the blood system), early febrile seizures, mitochondrial dysfunction, and neurologic disorders in CHEU¹⁵⁷⁻¹⁶⁰. Although some studies have reported that longer duration of perinatal ART exposure and atazanavir-based ART regimens have been associated with lower language scores among CHEU at 12 months, other studies at 24 months have found no notable differences ^{29,30,161,162}. In a study among CHEU from Botswana, *in utero* exposure to efavirenz (EFV)-based regimens was associated with neurodevelopmental deficits by age two, compared to non-EFV-based regimens ¹¹⁰. The World Health Organization (WHO)'s recommendation to transition all adolescents and adults living with HIV to the superior dolutegravir (DTG)-based regimens provides a unique opportunity to assess the impact of improved maternal ARV regimens on child neurodevelopment outcomes ¹⁰⁹. Ultimately, the benefits of administering ART for maternal HIV treatment and infant prophylaxis to prevent vertical transmission greatly outweigh the risks of rare and modest adverse outcomes; systemically employing rigorous scientific practices to identify the safest drugs for use in pregnancy and the postnatal period for women living with HIV is of paramount importance ¹⁶².

Brain maturation

Rapid brain growth in the first 1,000 days of life is vital for the development of healthy cognitive systems^{33,163}. Total grey matter and the basal ganglia are fundamental for neurodevelopment (e.g., social, motor, language, and memory skills), and structural alterations are associated with increased risk for neurologic disorders (e.g., autism spectrum disorder, attention-deficit disorders, schizophrenia)¹⁶³⁻¹⁶⁶. A recent magnetic resonance imaging (MRI) study in South Africa observed that newborn ART-exposed CHEU had significantly lower volumes of total grey matter and decreased size of caudate nucleus, a key component of the basal ganglia, compared to CHUU³³. This association was strongest when mothers had lower CD4 cell counts at delivery, stressing the importance of optimized HIV management and viral suppression during pregnancy³³. Other MRI studies comparing older CHEU and CHUU detected significantly altered basal ganglia neurotransmitters (regulators of movement, emotion, and language), choline (regulator of mood and intelligence), and creatine (regulator of energy production) among CHEU^{33,167-169}. Perinatal HIV exposure has also been found to be associated with neurometabolic patterns indicative of neuroinflammation, which may increase risk of neurodevelopmental delay among CHEU¹⁷⁰. Another study using diffusion tensor imaging revealed altered white matter microstructural integrity, essential for visuospatial and memory cognition, among CHEU¹⁷¹. More brain imaging studies with longer-term follow-up into early adulthood are needed to elucidate the significance of these findings in terms of individual neurodevelopmental and learning capabilities in settings with high prevalence of children, adolescents, and young adults who are HIV-exposed.

Birth outcomes, growth, and nutrition

Compared to HIV-unexposed children, CHEU are twice as likely to be born preterm and have a low birth weight, as well as face significantly higher prevalence of childhood inflammation, stunting, wasting, and microcephaly^{26,130,151,172-175}. Among CHEU, adverse birth outcomes such as prematurity (<37 weeks completed gestational age) and low birth weight (<2,500 grams) are associated with worse neurodevelopmental outcomes¹³⁷. Predictors of growth faltering among CHEU include lower maternal education, alcohol use during pregnancy, delivery by cesarean section, preterm birth, non-exclusive or shorter duration of breastfeeding, diarrheal episodes, and longer ART exposure during gestation¹⁷⁶⁻¹⁸⁰. In South Africa, preterm birth modified the relationship between perinatal HIV-exposure and poor neurodevelopment; similar odds of delay were observed between CHEU and CHUU born at term, but preterm CHEU had five times higher odds of delay compared to preterm CHUU¹³⁷. Separately, exclusive, prolonged breastfeeding has been shown to improve child growth and neurodevelopmental outcomes^{135,181}. However, although CHEU are often more likely to be exclusively breastfed and have longer breastfeeding durations than CHUU, CHEU remain at higher risk of undernutrition, poorer growth and

infectious morbidity in South Africa, Kenya, and other SSA settings ^{182,183}. Vigilant monitoring of nutrition and growth should be prioritized for CHEU, alongside access to nutritional support and food supplementation programs.

Home environment and caregiving

Households affected by HIV in SSA face multifactorial health and social disparities, including greater food insecurity and crowding compared to the general population ^{135,184}, which significantly predict poorer neurodevelopment among CHEU ^{29-31,107}. Additionally, CHEU have disproportionately lower access to safe water, sanitation, and hygiene (WASH) and adequate nutritional diversity. In the Zimbabwean SHINE Trial, CHEU randomized to a combined infant and young child feeding (IYCF) supplementation and WASH intervention performed significantly better on neurodevelopmental assessments compared to the standard of care arm; children randomized to either IYCF or WASH alone did not exhibit neurodevelopmental improvements, demonstrating the importance of joint interventions ^{185,186}. Interestingly, early child interventions that target caregivers through improved knowledge about responsive interaction, at-home stimulation, and providing a safe and healthy home environment, have shown to be significantly more impactful in promoting healthy child neurodevelopment compared to interventions that target the child through improved nutrition, water, and sanitation; but this has yet to be studied among CHEU ^{104,187}. Nonetheless, there is strong evidence that supports targeting both parents and children simultaneously to improve outcomes ¹⁸⁸. An extensive meta-analysis of over a hundred unique RCTs testing parenting interventions in 33 countries concluded that implementing interventions with curriculum on responsive caregiving and infant stimulation techniques, such as book-sharing, significantly improved parental knowledge, frequency and quality of interactions, and child neurodevelopment across all domains ^{104,189}. These findings were supported by a separate meta-analysis of 21 RCTs in low- and middle-income countries, which additionally found that parent-targeted interventions had the greatest impact on child neurodevelopment when delivered to parents living in rural areas with lower education, and when delivered in high doses of group sessions, as opposed to lower doses of individual sessions ^{190,191}.

Healthy parental relationships and paternal engagement in caregiving can significantly improve child health and neurodevelopment ^{5,37,124}. The home environment, including parental relationship stability, mental health, and exposure to household violence, can all impact a caregiver's ability to care responsively for their children ^{15,125,192}. Parenting couples affected by HIV frequently experience relationship tension and dissolution, and on average, HIV serodifferent couples separate five times more often when the female is the one living with HIV compared to the male ^{13,108}. Women living with HIV are

at high risk of stress, anxiety, depression and suicidal ideation^{39,193}, and studies have consistently found a strong relationship between maternal HIV, distress, and poor child neurodevelopmental outcomes^{35,36,40}. Poor maternal mental health can reduce the quantity and quality of parent-child interactions, diminishing a child's exposure to responsive caregiving and early learning opportunities³⁴. Women living with HIV also experience high rates of intimate partner violence (IPV), which can considerably threaten a child's neurodevelopment and academic performance^{14-17,37-39,46,77-79,124,125,192,194}. Separation is a desirable outcome for mothers living with HIV seeking to escape abusive or financially dependent relationships¹⁰⁸. Co-parenting, as opposed to parents staying together with persistent conflict or abuse, has been found to improve child neurodevelopmental outcomes, but has yet to be investigated in the SSA context^{98,99}. Despite the critical impact that caregiver relationships and mental health have on child development, mental health screening and relationship counseling are rarely implemented in low-resource settings where health care cadre are often overtasked¹⁹⁵. Thus, violence in HIV-affected homes, relationship conflict, and paternal disengagement could further contribute to suboptimal neurodevelopment among CHEU but remains understudied. Further research integrating quantitative and qualitative research methods are needed to assess the impact of home environment and caregiver factors on child neurodevelopment among families affected by HIV.

Programmatic support for CHEU

Building a comprehensive monitoring pathway for CHEU that leverages existing HIV-oriented programs is a promising route to consider. Ideally, HIV services and programs could adopt a structured early child development training program to train healthcare workers to conduct rapid neurodevelopmental screening tests based on milestones, detect even subtle "red flags," and offer immediate recommendations to caregivers to prevent or treat early delays using at-home stimulation techniques to improve cognitive functioning¹⁸⁸. Training videos for mothers in clinic waiting areas that demonstrate responsive caregiving techniques and home detection for early delays have also shown to improve child neurodevelopmental outcomes¹⁹⁶. Routine neurodevelopmental screenings should coincide with routine pediatric care visits, when the child is already receiving immunizations and growth monitoring, to reduce the burden on caregivers and healthcare workers¹⁸⁸. Mothers attending HIV services could also receive brief trainings or materials at each antenatal and postnatal visit about the importance of responsive caregiving, maternal mental health, WASH, and diverse nutrition (and if needed, food supplementation). Delivering these interventions early when CHEU families are actively engaged in care is paramount for maximizing immediate benefits and reducing loss to follow up^{104,187,197}. 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 treatments.

Fortunately, there are efficacious evidence-based treatments for children with developmental disabilities in high HIV burden settings which could be adopted ¹⁹⁷⁻¹⁹⁹. Iterative input from key stakeholders like in-country HIV and pediatric care decision-makers, health providers and caregivers will be fundamental for designing, delivering and monitoring these programs. Most importantly, rigorous research that generates local evidence will be critical to secure governmental buy-in and financial support, both essential for successful implementation and sustainability of such programs for CHEU.

CONCLUSION

Biological and sociodemographic factors can collectively contribute putative insults to child development, starting with the *in utero* milieu and progressing to household and caregiver specific factors. 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. Caregivers and providers need viable mechanisms and pathways to identify and support children at highest risk for poor outcomes. Early, multisectoral and impactful interventions and systematic follow up are urgently needed to ensure that all CHEU attain optimal neurodevelopmental maturation.

Acknowledgements: We would like to thank and acknowledge the numerous researchers and clinicians from around the world who contributed to the body of literature summarized in this commentary.

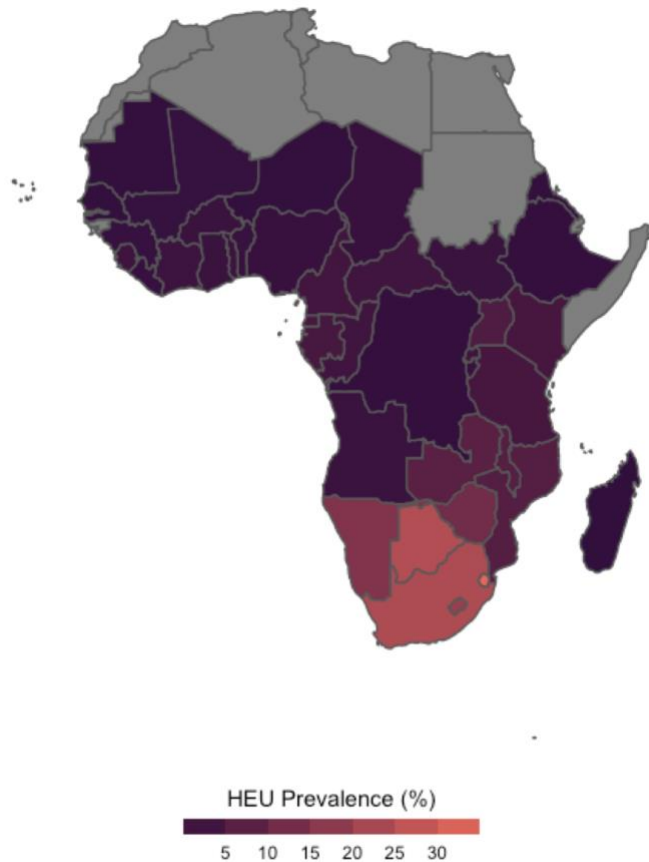
Conflict of Interest: The authors have no conflicts of interest to disclose.

Author Contributions: The initial topic of this commentary was developed by MB and GJS. MB led manuscript development with detailed guidance and iterative feedback from GJS, MM, LAG, KP, and CJW. All authors reviewed the manuscript several times and approved it for publication.

CHAPTER III: FIGURES

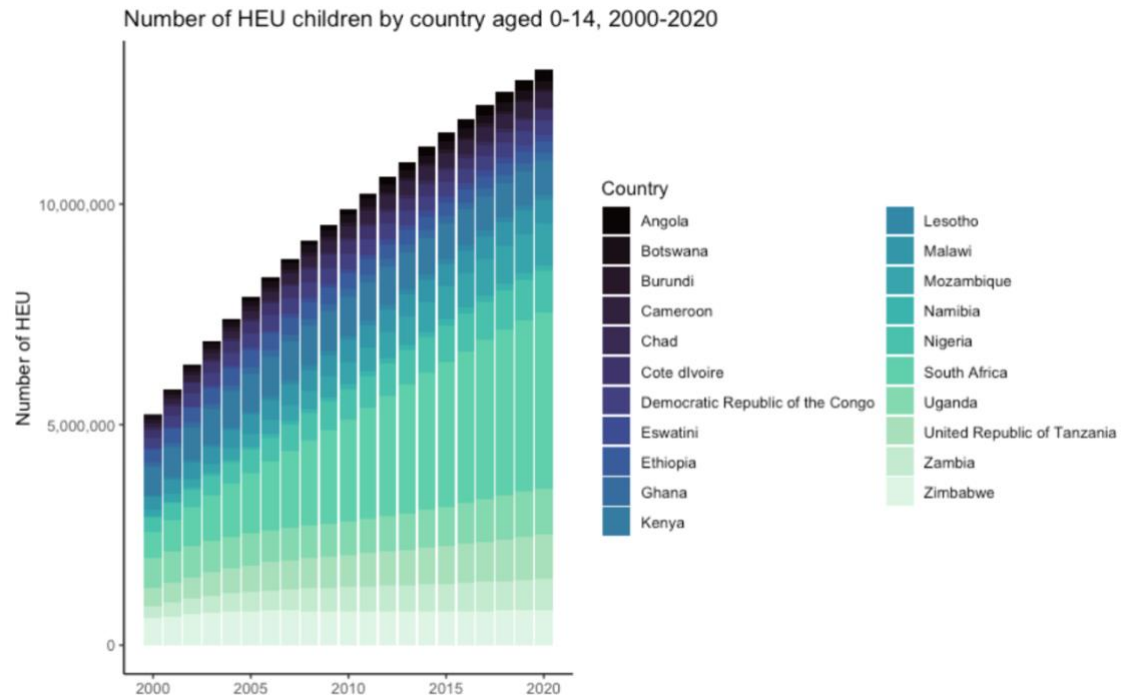
Figure 1. (a) Geographic heat map of reported prevalence of children who are HEU populations across sub-Saharan African countries, using UNAIDS Spectrum 2021 estimates. (b) Bar chart of population sizes of children who are HEU aged 0-14 years, from 2000-2020 by sub-Saharan African country. (c) Biologic and behavioral mechanistic pathways through which HEU status might impact neurodevelopment.

a.



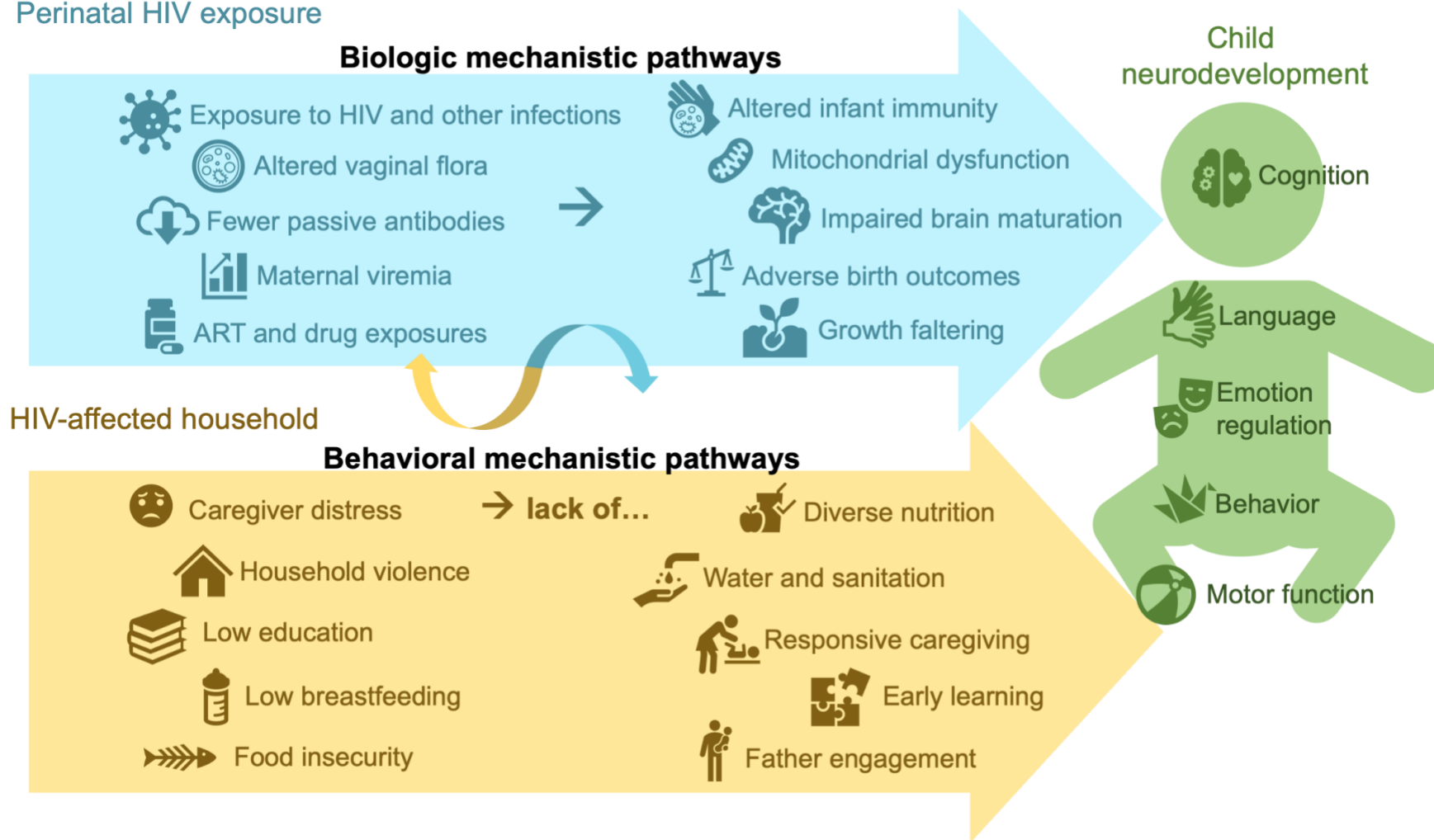
Data Source: **UNAIDS SPECTRUM 2021** Estimates

b.



c.

Perinatal HIV exposure



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