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School readiness among children born to women living with HIV in Dar es Salaam, Tanzania: a cohort study protocol

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Abstract

Introduction: Children who are born to women living with HIV are at a greater risk of suboptimal neurodevelopment; however, evidence from sub-Saharan Africa is limited and functional developmental outcomes are rarely assessed in this vulnerable population. The School Readiness among HIV-Exposed Children (SRHEC) cohort study aims to assess the school readiness of pre-school aged children born to women living with HIV and to identify the biological, environmental, and social factors that contribute to school readiness in this population.

Methods and analysis: The SRHEC cohort is an observational follow-up study of children born to HIV-infected pregnant women who were previously enrolled in a maternal vitamin D supplementation randomized, placebo-controlled trial in Dar es Salaam, Tanzania. This parent trial enrolled 2,300 pregnant women and followed mothers and infants up to one year postpartum. Mother/caregiver and child pairs will be eligible for the SRHEC follow-up study if the child is between 3-6.5 years of age at assessment, and the mother/caregiver provides informed consent. The International Development and Early Learning Assessment (IDELA) tool will be used to assess children's school readiness, including their early literacy, early numeracy, motor, social-emotional, and executive function skills. Data on maternal and child health and nutritional status (e.g., anthropometry, blood pressure, and diet) will be collected using standardized instruments and survey-based questionnaires. Data on maternal/caregiver depression and anxiety, maternal exposure to intimate partner violence, and HIV-related stigma will also be collected. Generalized linear and logistic regressions will be used to assess the relationship between child school readiness and biological, social, environmental factors.

Ethics and Dissemination: This study received ethical clearance from the Tanzanian National Institute of Medical Research, the Muhimbili University Health and Allied Sciences, and the Harvard T.H. Chan School of Public Health. We will disseminate our results in the form of scientific conference presentations and peer-reviewed publications.

What is already known on this topic

- With increasing availability of antiretroviral therapy for HIV-infected pregnant women in low-resource settings, the number of children who are HIV-exposed but uninfected (HEU) is increasing.
- HEU children are at a greater risk of suboptimal growth and development; however, evidence to date has been primarily from high-income settings.
- Furthermore, functional developmental outcomes, such as school readiness, are rarely assessed in HIV-affected pediatric populations.

What this study hopes to add

- This prospective cohort study aims to assess the school readiness of pre-school aged children born to women living with HIV in Dar es Salaam, Tanzania.
- The study also aims to identify the biological, environmental, and social factors that contribute to school readiness in this population.
- Study findings will provide robust data for designing interventions to support school readiness and ensure optimal growth and development outcomes among HIV-affected children.

Introduction

In 2015, the World Health Organization (WHO) released guidelines, known colloquially as "Option B+", which recommended that all pregnant and breastfeeding women with human immunodeficiency virus (HIV) should initiate lifelong antiretroviral therapy (ART), regardless of HIV disease stage, to prevent mother-to-child transmission and sexual transmission of HIV, and to improve maternal clinical outcomes.[1] With global efforts continuing to increase the availability of and access to ART for women living with HIV in low-resource settings, the number of children who are HIV exposed, but uninfected (HEU) is increasing. Globally, 14.8 million children aged 0 to 14 years are estimated to be HEU, 13.2 million of whom reside in sub-Saharan Africa.[2] The number of HEU children has increased between 100% to ~800% in the highest burden countries in sub-Saharan Africa since 2000.[3]

Evidence primarily from in high-income settings suggests that children who are born to women living with HIV are at a greater risk for suboptimal cognitive, motor, behavioral, and socioemotional development as compared to their HIV-unexposed peers.[4–6] Biological risk factors, such as exposure to HIV and ART in-utero, increased risk of maternal illness, poor nutrition during pregnancy, and increased risk of being born low birthweight or preterm have been associated with higher risk of poor development among young children.[7,8] Numerous social, economic, and environmental factors related to living in an HIV-affected household, such as parental mental health and depression, stigma, reduced parental attention, and reduced availability of resources and income are also likely to influence children's development.[4,5] However, the relative contribution of the biological and social, socioeconomic and environmental risk factors on the risk of suboptimal developmental outcomes of HIV-affected children in the context of sub-Saharan Africa remains unclear. In addition, few studies have examined the functional outcomes related to early development, such as school readiness, which comprises of a range of both academic and non-academic early learning and developmental skills that support successful engagement in schools, among HIV-affected children.

The Sustainable Development Goal (SDG) Target 4.2 calls for all girls and boys to have access to quality early childhood development, care, and pre-primary education to ensure that they are ready for primary education.[9] Given the known developmental inequities faced by young HIV-affected children, there is an urgent need to understand what factors influence school readiness among HIV-affected children and to develop and implement interventions to support school readiness in this vulnerable population. To this end, the School Readiness among HIV-Exposed Children (SRHEC) cohort study aims to assess the development and school readiness of pre-school aged children born to women living with HIV in Dar es Salaam, Tanzania, and to identify the biological, social, and environmental risk and protective factors that contribute to the school readiness in this population. The findings from this study will provide a unique opportunity to disentangle the multi-faceted relationships that influence child school readiness in HIV-affected pediatric populations, and to identify points of intervention to support child development.

Methods

Parent trial and cohort study design

The SRHEC cohort study is a cross-sectional follow-up of children born in an individually randomized double-blind, placebo-controlled trial of maternal vitamin D_3 (cholecalciferol) supplementation conducted among pregnant women living with HIV in Dar es Salaam, Tanzania (ClinicalTrials.gov: NCT02305927). The detailed protocol of the trial, which was conducted between 2015-2019, has been published elsewhere.[10,11] Briefly, the parent trial enrolled 2300 pregnant women living with HIV, who were ≥18 years of age, in the second trimester of pregnancy (12 – 27 weeks gestational age), and receiving ART, to investigate whether daily vitamin D supplementation (3000 IU/day) could provide a low-cost adjunct intervention to improve maternal and child health outcomes. Pregnant women were enrolled in the trial from five public antenatal care clinics that provided antenatal care for pregnant women living with HIV. During the trial, Tanzania used the Option B+ approach, where all pregnant women living with HIV were initiated on lifelong triple-drug ART, irrespective of CD4 T-cell counts or HIV disease stage. The first line of ART during the trial was tenofovir/lamivudine/efavirenz, which was used by 99% of women in the

trial during pregnancy and the first year postpartum. Participants were followed at monthly visits during the prenatal period, at delivery, at 6, 10, and 14 weeks postpartum, and monthly thereafter up to 12 months postpartum. Detailed information on maternal sociodemographic characteristics, clinical outcomes (including HIV disease stage), nutrition status, and depressive symptoms were collected during the prenatal period. In the postpartum period, mothers' follow-up assessments included clinical examination, HIV disease stage assessment, and anthropometric measurement. Child follow-up assessments included detailed clinical examination, infant feeding practices, and anthropometry, as well as child development at the last visit. The primary outcomes of the trial were maternal HIV progression or death from any cause, small-for-gestational age (SGA) births, and infant stunting (length-for-age z-score <-2 standard deviation from the median of the reference population) at 12 months of age. Vitamin D supplementation had no effect on the primary trial outcomes.[11]

Participant eligibility for follow up

All mother-child pairs who previously participated in the trial of maternal vitamin D supplementation will be eligible for inclusion in the SRHEC follow-up study if: (i) child age is between 3 to 6.5 years at the time of assessment, and (ii) the mother/caregiver provides informed consent. For a child whose mother was enrolled in the trial of vitamin D supplementation but was not available for the follow-up study (e.g., due to death), we will ask the child's current primary caregiver for consent to participate. We will use information collected during the parent trial to invite women previously enrolled in the parent trial for the follow-up study. Mother/caregiver and child pairs will be invited to the study clinics to learn more about the follow-up study and for study assessments if they agree to participate. Women who previously withdrew from the parent trial or who were lost to follow-up during the trial period, which was until 1-year postpartum, will not be contacted. Written informed consent will be obtained from all participants in Kiswahili.

Study procedures and assessments

Eligible mother/caregiver and child pairs who consent to participate in the follow-up study will be assessed in quiet rooms at study clinics in tertiary hospitals in Dar es Salaam, Tanzania. For each mother/caregiver and child pair we will collect detailed information on various domains, including sociodemographic factors, nutritional status, mental health status, and child development and school readiness (Table 1). Tools and procedures used to measure each of these domains are described below.

Table 1: Types of assessment planned for mother/caregiver and child pairs.

Assessment components	Mother/Caregiver*	Child
Sociodemographic characteristics	x	
Health and nutritional status	x	x
Parenting practices	x	
Mental health	x	
Social support	x	
Intimate partner violence	x	
HIV-stigma	x	
Early learning and development		
International Development and Early Learning Assessment		x
Early Child Development Index 2030		x
Strengths and Difficulties questionnaire		x

*Caregiver assessments will not include the health and nutritional status and the intimate partner violence and HIV-stigma components.

(i) Child development and school readiness: We will use the International Development and Early Learning Assessment (IDELA) tool developed by Save the Children to assess school readiness in young children aged 3 to 6.5 years in low-resource settings.[12] Briefly, the IDELA is a tool with 22 subtasks that is easily-administered, holistic, rigorous, culturally adaptable and open-source, used to assess four core domains: (1) motor development, (2) emergent literacy, (3) emergent numeracy, (4) social-emotional development, plus an optional module on (5) executive functioning (i.e., short-term memory, inhibitory control, sustained attention). The IDELA is designed to capture broadly cross-culturally relevant skills

that support children's transition into formal learning environments in school. It is administered on a one-on-one basis, does not require specific disciplinary trainings, and is administered using a minimal set of materials: a pencil, blank paper, small items for counting (such as beans or buttons), nine picture cards, and a storybook. The IDELA tool has been previously adapted for and used in Tanzania.[13] We will assess inter-rater reliability for 5% of IDELA assessments selected at random.

As a secondary measure of development, we will implement the Early Child Development Index 2030 (ECDI2030), which is commonly used in population-based surveys to assess whether a child is meeting expected developmental milestones in motor, language, math, literacy, executive functioning, and socio-emotional domains.[14] The ECDI2030 is used to evaluate progress towards SDG target 4.2 and is administered as 20 close-ended questions to the mother or primary caregiver, where they indicate whether their child has exhibited behaviors in each question. We will also use the Strengths and Difficulties Questionnaire (SDQ), which has previously been implemented in Tanzania, to assess children's overall mental health status as indexed by internalizing and externalizing behaviors.[15] Like the ECDI2030, the SDQ is a mother/caregiver-reported instrument; it includes 25 items rated on a Likert-like scale assessing frequency of behavior.[16] All child development and school readiness tools will be administered by nurses, who will be trained using the standard training procedures for each tool.

(ii) Maternal and child health and nutrition: We will use standardized procedures to measure anthropometry. Maternal and child weight will be measured using electronic floor scale (ADE M320600, Germany) with 50 g precision up to 50 kg, and 100 g precision thereafter. Participants will be requested to remove shoes and wear light clothing at the time of weight measurement. Maternal and child standing height will be measured using a stadiometer (ADE Mechanical Height MZ10017, Germany) with 1mm precision and mid-upper arm circumference (MUAC) will be measured using a circumference tap measure (ADE MZ10021, Germany) with 1mm precision. Child head circumference will be measured using a Schorr tape with 1 mm precision. All child anthropometric measures will be taken in triplicate and

maternal measures will be recorded in duplicate. In addition to anthropometry, we will measure maternal blood pressure in duplicate, using a digital blood pressure machine (OMRON BP7200) with free-size cuff, with participant in a seated position after five minutes of rest. Anthropometric equipment will be calibrated daily, and the blood pressure monitor will be calibrated every month using a manual mercury sphygmomanometer. Minimum dietary diversity for women of reproductive age (MDD-W) will be assessed using the Food and Agriculture Organization guidelines.[17] Child diet will be assessed using a modified 24-hour recall for infant and young child feeding practices (removing any items relevant to children <2 years of age only) where mothers/caregivers are asked about the types of foods consumed by the child in the last 24 hours to record the food groups.[18] We will also assess child's current health status as measured by episodes of morbidity, such as diarrhea and fever, in the two-week period prior to the assessment.

(iii) Maternal/Caregiver mental health and social support: Maternal depression will be assessed using the Hopkins Symptom Checklist (HSCL-25), which is comprised of 15 items on depressive symptoms and 10 items on anxiousness symptoms; it has previously been validated for use in Tanzania among pregnant women living with HIV.[19] We will also measure the mother's perception of social support using an adapted Duke University–University of North Carolina Functional Social Support Questionnaire, consisting of 8 questions to measure constructs of support from confidants and affective support.[20] The tool has been previously adapted for use in Tanzania and can be used to distinguish between two underlying constructs of instrumental and emotional support.[21] We will also measure depression and perception of social support for primary caregivers, should the mother be unavailable.

(iv) Maternal HIV-related stigma and intimate partner violence (IPV): We will measure mothers' reports of HIV-related stigma using an abbreviated version the Berger scale,[22] which has been previously used in Tanzania,[23,24] and consists of 7 questions to capture internalized stigma (shame, guilt) and

externalized stigma as experienced by treatment from other people who are aware of the respondent's HIV status. We will also assess prevalence of IPV, which in this context is most commonly directed towards women by male partners. IPV has been described to manifest in a range of behaviors, including but not limited to: physical, sexual, emotional or psychological, and controlling behaviors that include restricting financial or economic independence.[25] Physical and sexual aspects of IPV will be assessed using an abbreviated mother-reported IPV module found in the Tanzania Demographic and Health Survey and has been previously used in other studies.[26,27] Emotional and economic aspects of IPV will be assessed using abbreviated questions that were previously used in Tanzania.[28] We will not assess HIV-related stigma or IPV for caregivers.

(v) Caregiving practices and resources for learning: Caregiving practices, including disciplinary practices, such as corporal punishment, and responsive caregiving and stimulation practices (e.g., reading, counting, playing), will be measured using the mother/caregiver-reported Family Care Indicators taken from the Multiple Indicator Cluster Surveys.[29,30] We will also collect data on resources available for learning, such as books and toys, to assess children's learning environment at home, using items from the Family Care Indicators.

(vi) Maternal HIV variables at time of assessment: We will seek consent to retrieve mother's medical information from the HIV treatment clinic and to link HIV treatment information, including information on HIV disease stage based on the WHO classification, history of ART regimens, viral load and laboratory results.

(vii) Data collected during pregnancy and first year postpartum: We will link the maternal/caregiver and child data collected in this study with existing data from parent vitamin D supplementation trial to assess long-term associations of maternal and child perinatal health with child development and school readiness in the pre-school years.

Safety procedures and referrals

All research staff will be trained in a 2-week training workshop where they will learn about and familiarize themselves with all study procedures, including the planned referral scheme and supports that will be made available to participants and their children. Study staff members will also be trained in referring study mothers/caregivers for mental health care if they report IPV or depression. If signs of suicidality are reported, mothers/caregivers will be kept under observation until they are seen by a clinical psychiatrist and referred for mental health services. Mothers/caregivers and their children will be referred to clinical and nutritional services at the hospital if undernutrition and malnutrition are detected. We will follow strict safety precautions and procedures (e.g., masks, hand sanitizers) to prevent the transmission of COVID-19 among the study staff and participants.

Sample size

All mother and infant pairs who were discharged from the parent trial at 12 months postpartum (n = 2053) will be eligible for the SRHEC follow-up study and will be invited to participate in the study.

Quality assurance and data management

Standardization sessions will be held every 3 months to ensure the data collectors are following the recommended techniques, to monitor reliability (precision and accuracy), and to take corrective measures if required. Data queries will be regularly generated and checked by study field staff as part of quality assurance/quality control measures to detect outliers and possible erroneous values.

Statistical analysis

We will generate summary statistics, including means and proportions, of child outcome domains as described in the standard methodology for the IDELA, ECDI2030, and SDQ measures including both domain-level and overall scores where appropriate. Subscale scores for caregiving practices, resources for

learning, maternal depression, and anxiety, will be similarly derived using internationally validated standards and cutoffs when available, and sum scores or z-scores as relevant. Child growth will be assessed using standardized indices and indicators of anthropometric measures using the World Health Organization Child Growth Standards.[31,32] Scores for child development and school readiness will be converted to z-scores based on study sample distribution with a mean of 0 and an SD of 1 for analysis. We will estimate differences in child health, nutrition, development and school readiness outcome scores across different exposures of interest using generalized linear regression models. Relationships with categorial indicators of suboptimal child development will be estimated using modified Poisson regression with robust standard errors. All regression models will be adjusted for potential sociodemographic confounders, such as child age, child sex, maternal/caregiver age, household wealth quintile, and number of children in the household, among others.

Ethics and dissemination

This study received ethical clearance from the Tanzanian National Institute of Medical Research, the Muhimbili University Health and Allied Sciences, and the Harvard TH Chan School of Public Health. Permission to conduct the study was granted by the President's Office, Regional Administration and Local Government (PORALG) and the Regional Medical Officer (RMO) of Dar-es-Salaam. We will disseminate our results in the form of scientific conference presentations, presentations to the RMO, and as peer-reviewed publications.

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Authors' contributions

NP, AR, DM, JS, CRS, KM contributed to the study conceptualization, and all authors contributed to the study design and data collection. NP drafted the initial manuscript and revised the paper. All authors contributed to revising the manuscript for important intellectual content and have read and approved the final manuscript.

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Competing interests statement

The authors have no competing interests to declare.

Patient and public involvement: Patients and/or the public were not involved in the design of the study, but are involved in the conduct of and the dissemination plans of this research.

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School readiness among children born to women living with HIV in Dar es Salaam, Tanzania: a cohort study protocol

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Abstract

Introduction: Children who are born to women living with HIV are at a greater risk of suboptimal neurodevelopment; however, evidence from sub-Saharan Africa is limited and functional developmental outcomes are rarely assessed in this vulnerable population. The School Readiness among HIV-Exposed Children (SRHEC) cohort study aims to assess the school readiness of pre-school aged children born to women living with HIV and to identify the biological, environmental, and social factors that contribute to school readiness in this population.

Methods and analysis: The SRHEC cohort is an observational follow-up study of children born to HIV-infected pregnant women who were previously enrolled in a maternal vitamin D supplementation randomized, placebo-controlled trial in Dar es Salaam, Tanzania. This parent trial enrolled 2,300 pregnant women and followed mothers and infants up to one year postpartum. Mother/caregiver and child pairs will be eligible for the SRHEC follow-up study if the child is between 3-6.5 years of age at assessment, and the mother/caregiver provides informed consent. The International Development and Early Learning Assessment (IDELA) tool will be used to assess children's school readiness, including their early literacy, early numeracy, motor, social-emotional, and executive function skills. Data on maternal and child health and nutritional status (e.g., anthropometry, blood pressure, and diet) will be collected using standardized instruments and survey-based questionnaires. Data on maternal/caregiver depression and anxiety, maternal exposure to intimate partner violence, and HIV-related stigma will also be collected. Generalized linear and logistic regressions will be used to assess the relationship between child school readiness and biological, social, environmental factors.

Ethics and Dissemination: This study received ethical clearance from the Tanzanian National Institute of Medical Research, the Muhimbili University Health and Allied Sciences, and the Harvard T.H. Chan School of Public Health. We will disseminate our results in the form of scientific conference presentations and peer-reviewed publications.

What is already known on this topic

- With increasing availability of antiretroviral therapy for HIV-infected pregnant women in low-resource settings, the number of children who are HIV-exposed but uninfected (HEU) is increasing.
- HEU children are at a greater risk of suboptimal growth and development; however, evidence to date has been primarily from high-income settings.
- Furthermore, functional developmental outcomes, such as school readiness, are rarely assessed in HIV-affected pediatric populations.

What this study hopes to add

- This prospective cohort study aims to assess the school readiness of pre-school aged children born to women living with HIV in Dar es Salaam, Tanzania.
- The study also aims to identify the biological, environmental, and social factors that contribute to school readiness in this population.
- Study findings will provide robust data for designing interventions to support school readiness and optimal growth and developmental outcomes among HIV-affected children.

Introduction

In 2015, the World Health Organization (WHO) released guidelines, known colloquially as "Option B+", which recommended that all pregnant and breastfeeding women with human immunodeficiency virus (HIV) should initiate lifelong antiretroviral therapy (ART), regardless of HIV disease stage, to prevent mother-to-child transmission and sexual transmission of HIV, and to improve maternal clinical outcomes.[1] With global efforts continuing to increase the availability of and access to ART for women living with HIV in low-resource settings, the number of children who are HIV exposed, but uninfected (HEU) is increasing. Globally, 14.8 million children aged 0 to 14 years are estimated to be HEU, 13.2 million of whom reside in sub-Saharan Africa.[2] The number of HEU children has increased between 100% to ~800% in the highest burden countries in sub-Saharan Africa since 2000.[3]

Evidence primarily from in high-income settings suggests that children who are born to women living with HIV are at a greater risk for suboptimal cognitive, motor, behavioral, and socioemotional development as compared to their HIV-unexposed peers.[4–6] Biological risk factors, such as exposure to HIV and ART in-utero, increased risk of maternal illness, poor nutrition during pregnancy, and increased risk of being born low birthweight or preterm have been associated with higher risk of poor development among young children.[7,8] Numerous social, economic, and environmental factors related to living in an HIV-affected household, such as parental mental health and depression, stigma, reduced parental attention, and reduced availability of resources and income are also likely to influence children's development.[4,5] However, the relative contribution of the biological and social, socioeconomic and environmental risk factors on the risk of suboptimal developmental outcomes of HIV-affected children in the context of sub-Saharan Africa remains unclear. In addition, few studies have examined the functional outcomes related to early development, such as school readiness, which comprises of a range of both academic and non-academic early learning and developmental skills that support successful engagement in schools, among HIV-affected children.

The Sustainable Development Goal (SDG) Target 4.2 calls for all girls and boys to have access to quality early childhood development, care, and pre-primary education to ensure that they are ready for primary education.[9] Given the known developmental inequities faced by young HIV-affected children, there is an urgent need to understand what factors influence school readiness among HIV-affected children and to develop and implement interventions to support school readiness in this vulnerable population. To this end, the School Readiness among HIV-Exposed Children (SRHEC) cohort study aims to assess the development and school readiness of pre-school aged children born to women living with HIV in Dar es Salaam, Tanzania, and to identify the biological, social, and environmental risk and protective factors that contribute to the school readiness in this population. The findings from this study will provide a unique opportunity to disentangle the multi-faceted relationships that influence child school readiness in HIV-affected pediatric populations, and to identify points of intervention to support child development.

Methods

Parent trial and cohort study design

The SRHEC cohort study is a cross-sectional follow-up of children born in an individually randomized double-blind, placebo-controlled trial of maternal vitamin D_3 (cholecalciferol) supplementation conducted among pregnant women living with HIV in Dar es Salaam, Tanzania (ClinicalTrials.gov: NCT02305927). The detailed protocol of the trial, which was conducted between 2015-2019, has been published elsewhere.[10,11] Briefly, the parent trial enrolled 2300 pregnant women living with HIV, who were ≥18 years of age, between 12 – 27 weeks gestational age, and receiving ART, to investigate whether daily vitamin D supplementation (3000 IU/day) could provide a low-cost adjunct intervention to improve maternal and child health outcomes. Women were enrolled in the trial from five public antenatal care clinics that provided antenatal care for pregnant women living with HIV. During the trial, Tanzania used the Option B+ approach, where all pregnant women living with HIV were initiated on lifelong triple-drug ART, irrespective of CD4 T-cell counts or HIV disease stage. The first line of ART during the trial was tenofovir/lamivudine/efavirenz, which was used by 99% of women in the trial during pregnancy and the

first year postpartum. Participants were followed at monthly visits during the prenatal period, at delivery, at 6, 10, and 14 weeks postpartum, and monthly thereafter up to 12 months postpartum. Detailed information on maternal sociodemographic characteristics, clinical outcomes (including HIV disease stage), nutrition status, and depressive symptoms were collected during the prenatal period. In the postpartum period, mothers' follow-up assessments included clinical examination, HIV disease stage assessment, and anthropometric measurement. Child follow-up assessments included detailed clinical examination, infant feeding practices, and anthropometry, as well as child development assessed by the Caregiver-Reported Early Development Index[12] at the last visit. The primary outcomes of the trial were maternal HIV progression or death from any cause, small-for-gestational age (SGA) births, and infant stunting (length-for-age z-score <-2 standard deviation from the median of the reference population) at 12 months of age. Vitamin D supplementation had no effect on the primary trial outcomes.[11]

Participant eligibility for follow up

All mother-child pairs who previously participated in the trial of maternal vitamin D supplementation will be eligible for inclusion in the SRHEC follow-up study if: (i) child age is between 3 to 6.5 years at the time of assessment, and (ii) the mother/caregiver provides informed consent. For a child whose mother was enrolled in the trial of vitamin D supplementation but was not available for the follow-up study (e.g., due to death), we will ask the child's current primary caregiver for consent to participate. We will use information collected during the parent trial to invite women previously enrolled in the parent trial for the follow-up study. Mother/caregiver and child pairs will be invited to the study clinics to learn more about the follow-up study and for study assessments if they agree to participate. Women who previously withdrew from the parent trial or who were lost to follow-up during the trial period, which was until 1-year postpartum, will not be contacted. Written informed consent will be obtained from all participants in the local language of Kiswahili.

Study procedures and assessments

Eligible mother/caregiver and child pairs who consent to participate in the follow-up study will be assessed in quiet rooms at study clinics in tertiary hospitals in Dar es Salaam, Tanzania. For each mother/caregiver and child pair we will collect detailed information on various domains, including sociodemographic factors, nutritional status, mental health status, and child development and school readiness (Table 1). Tools and procedures used to measure each of these domains are described below.

Table 1: Types of assessment planned for mother/caregiver and child pairs.

Assessment components	Mother/Caregiver*	Child
Sociodemographic characteristics	x	
Health and nutritional status	x	x
Parenting practices	x	
Mental health	x	
Social support	x	
Intimate partner violence	x	
HIV-stigma	x	
Early learning and development		
International Development and Early Learning Assessment		x
Early Child Development Index 2030		x
Strengths and Difficulties questionnaire		x

*Caregiver assessments will not include the health and nutritional status and the intimate partner violence and HIV-stigma components.

(i) Child development and school readiness: We will use the International Development and Early Learning Assessment (IDELA) tool developed by Save the Children to assess school readiness in young children aged 3 to 6.5 years in low-resource settings.[13] Briefly, the IDELA is a tool with 22 subtasks that is easily-administered, holistic, rigorous, culturally adaptable and open-source, used to assess four core domains: (1) motor development, (2) emergent literacy, (3) emergent numeracy, (4) social-emotional development, plus an optional module on (5) executive functioning (i.e., short-term memory, inhibitory control, sustained attention). The IDELA is designed to capture broadly cross-culturally relevant skills

that support children's transition into formal learning environments in school. It is administered on a one-on-one basis, does not require specific disciplinary trainings, and is administered using a minimal set of materials: a pencil, blank paper, small items for counting (such as beans or buttons), nine picture cards, and a storybook. The IDELA is scored by calculating the average percentage of correct responses for each task within the four core domains (emergent numeracy, emergent literacy, motor, and social-emotional), and the overall IDELA score, ranging from 0 to 100%, is calculated as the average percentage for the four domain scores[13]. The IDELA tool has been previously adapted for and used in Tanzania.[14] We will assess inter-rater reliability for 5% of IDELA assessments selected at random.

As a secondary measure of development, we will implement the Early Child Development Index 2030 (ECDI2030), which is commonly used in population-based surveys to assess whether a child is meeting expected developmental milestones in motor, language, math, literacy, executive functioning, and socio-emotional domains.[15] The ECDI2030 is used to evaluate progress towards SDG target 4.2 and is administered as 20 close-ended questions to the mother or primary caregiver, where they indicate whether their child has exhibited behaviors in each question. The ECDI2020 indicator is defined as the proportion of children 24 to 59 months of age who have achieved the minimum number of milestones expected for their age according to age-specific cut-off scores compared to all children aged 24 to 59 months of age. We will also use the Strengths and Difficulties Questionnaire (SDQ), which has previously been implemented in Tanzania, to assess children's overall mental health status as indexed by internalizing and externalizing behaviors.[16] Like the ECDI2030, the SDQ is a mother/caregiver-reported instrument; it includes 25 items rated on a Likert-like scale assessing frequency of emotional problems, conduct problems, hyperactivity, peer-problems and prosocial behaviour.[17] The total difficulties score is generated by summing the scores from all scales except the prosocial scale. All child development and school readiness tools will be administered by nurses, who will be trained using the standard training procedures for each tool. Although primary school in Tanzania begins at age 7 and attendance in pre-school educational programs is rare in this population, we will also collect data on whether children enrolled in

the study attended primary school and had previously or currently attended pre-school education programs.

(ii) Maternal and child health and nutrition: We will use standardized procedures to measure anthropometry. Maternal and child weight will be measured using electronic floor scale (ADE M320600, Germany) with 50 g precision up to 50 kg, and 100 g precision thereafter. Participants will be requested to remove shoes and wear light clothing at the time of weight measurement. Maternal and child standing height will be measured using a stadiometer (ADE Mechanical Height MZ10017, Germany) with 1mm precision and mid-upper arm circumference (MUAC) will be measured using a circumference tap measure (ADE MZ10021, Germany) with 1mm precision. Child head circumference will be measured using a Schorr tape with 1 mm precision. All child anthropometric measures will be taken in triplicate and maternal measures will be recorded in duplicate. In addition to anthropometry, we will measure maternal blood pressure in duplicate, using a digital blood pressure machine (OMRON BP7200) with free-size cuff, with participant in a seated position after five minutes of rest. Anthropometric equipment will be calibrated daily, and the blood pressure monitor will be calibrated every month using a manual mercury sphygmomanometer. Minimum dietary diversity for women of reproductive age (MDD-W) will be assessed using the Food and Agriculture Organization guidelines, summing the total number of different food groups consumed.[18] Child diet will be assessed using a modified 24-hour recall for infant and young child feeding practices (removing any items relevant to children <2 years of age only) where mothers/caregivers are asked about the types of foods consumed by the child in the last 24 hours to record the food groups.[19] We will also assess child's current health status as measured by episodes of morbidity, such as diarrhea and fever, in the two-week period prior to the assessment.

(iii) Maternal/Caregiver mental health and social support: Maternal depression will be assessed using the Hopkins Symptom Checklist (HSCL-25), which is comprised of 15 items on depressive symptoms

and 10 items on anxiousness symptoms with each item having a possible score of 1-4 (1 = not at all; to 4 = extremely); it has previously been validated for use in Tanzania among pregnant women living with HIV.[20] We will also measure the mother's perception of social support using an adapted Duke University–University of North Carolina Functional Social Support Questionnaire, consisting of 8 questions graded on a 4-point Likert scale to measure constructs of support from confidants and affective support.[21] The tool has been previously adapted for use in Tanzania and can be used to distinguish between two underlying constructs of instrumental and emotional support.[22] We will also measure depression and perception of social support for primary caregivers, should the mother be unavailable.

(iv) Maternal HIV-related stigma and intimate partner violence (IPV): We will measure mothers' reports of HIV-related stigma using an abbreviated version the Berger scale,[23] which has been previously used in Tanzania,[24,25] and consists of 7 questions graded on a 5-point Likert scale to capture internalized stigma (shame, guilt) and externalized stigma as experienced by treatment from other people who are aware of the respondent's HIV status. We will also assess prevalence of IPV, which in this context is most commonly directed towards women by male partners. IPV has been described to manifest in a range of behaviors, including but not limited to: physical, sexual, emotional or psychological, and controlling behaviors that include restricting financial or economic independence.[26] Physical and sexual aspects of IPV will be assessed using an abbreviated mother-reported IPV module found in the Tanzania Demographic and Health Survey and has been previously used in other studies.[27,28] Emotional and economic aspects of IPV will be assessed using abbreviated questions that were previously used in Tanzania.[29] We will not assess HIV-related stigma or IPV for caregivers.

(v) Caregiving practices and resources for learning: Caregiving practices, including disciplinary practices, such as corporal punishment, and responsive caregiving and stimulation practices (e.g., reading, counting, playing), will be measured using the mother/caregiver-reported Family Care Indicators (FCI)

taken from the Multiple Indicator Cluster Surveys.[30,31] The FCI score will be a summative score based on responses (yes/no) for each individual item. We will also collect data on resources available for learning, such as books and toys, to assess children's learning environment at home.

(vi) Maternal HIV variables at time of assessment: We will seek consent to retrieve mother's medical information from the HIV treatment clinic and to link HIV treatment information, including information on HIV disease stage based on the WHO classification, history of ART regimens, viral load and laboratory results.

(vii) Data collected during pregnancy and first year postpartum: We will link the maternal/caregiver and child data collected in this study with existing data from parent vitamin D supplementation trial to assess long-term associations of maternal and child perinatal health with child development and school readiness in the pre-school years.

Safety procedures and referrals

All research staff will be trained in a 2-week training workshop where they will learn about and familiarize themselves with all study procedures, including the planned referral scheme and supports that will be made available to participants and their children. Study staff members will also be trained in referring study mothers/caregivers for mental health care if they report IPV or depression. If signs of suicidality are reported, mothers/caregivers will be kept under observation until they are seen by a clinical psychiatrist and referred for mental health services. Mothers/caregivers and their children will be referred to clinical and nutritional services at the hospital if undernutrition and malnutrition are detected. We will follow strict safety precautions and procedures (e.g., masks, hand sanitizers) to prevent the transmission of COVID-19 among the study staff and participants.

Sample size

All mother and infant pairs who were discharged from the parent trial at 12 months postpartum (n = 2053) will be eligible for the SRHEC follow-up study and will be invited to participate in the study.

Quality assurance and data management

Standardization sessions will be held every 3 months to ensure the data collectors are following the recommended techniques, to monitor reliability (precision and accuracy), and to take corrective measures if required. Data queries will be regularly generated and checked by study field staff as part of quality assurance/quality control measures to detect outliers and possible erroneous values.

Statistical analysis

We will generate summary statistics, overall and by age-strata, of child outcome domains as described in the standard methodology for the IDELA, ECDI2030, and SDQ measures including both domain-level and overall scores where appropriate. Subscale scores for caregiving practices, resources for learning, maternal depression, and anxiety, will be similarly derived using internationally validated standards and cutoffs when available, and summative scores or z-scores as relevant. Child growth will be assessed using standardized indices and indicators of anthropometric measures using the World Health Organization Child Growth Standards.[32,33] Scores for child development and school readiness will be converted to overall z-scores based on study sample distribution with a mean of 0 and an SD of 1 for analysis. Using these standardized scores, we will assess the relationship between early child development assessed in the parent trial, at approximately 12 months of age, and school readiness. We will also estimate differences in child health, nutrition, development and school readiness outcome scores across different exposures of interest using generalized linear regression models. Child age will be included as a confounder or effect modifier in all regression analysis, as appropriate. Relationships with categorial indicators of suboptimal child development will be estimated using modified Poisson regression with robust standard errors. All regression models will be adjusted for potential sociodemographic confounders, such as child age, child

sex, maternal/caregiver age, household wealth quintile, and number of children in the household, among others.

Ethics and dissemination

This study received ethical clearance from the Tanzanian National Institute of Medical Research, the Muhimbili University Health and Allied Sciences, and the Harvard TH Chan School of Public Health. Permission to conduct the study was granted by the President's Office, Regional Administration and Local Government (PORALG) and the Regional Medical Officer (RMO) of Dar-es-Salaam. We will disseminate our results in the form of scientific conference presentations, presentations to the RMO, and as peer-reviewed publications.

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Authors' contributions

NP, AS, DM, JS, CRS, KM contributed to the study conceptualization, and all authors contributed to the study design and data collection. NP drafted the initial manuscript and revised the paper. All authors contributed to revising the manuscript for important intellectual content and have read and approved the final manuscript.

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Competing interests statement

The authors have no competing interests to declare.

Patient and public involvement: Patients and/or the public were not involved in the design of the study, but are involved in the conduct of and the dissemination plans of this research.