BMJ Open

Predicting neurodevelopmental risk in children born to mothers living with HIV in Kenya: protocol for a prospective cohort study (Tabiri Study)

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To cite: Oyungu E, El Kebbi O, Vreeman R, *et al*. Predicting neurodevelopmental risk in children born to mothers living with HIV in Kenya: protocol for a prospective cohort study (Tabiri Study). *BMJ Open* 2022;**12**:e061051. doi:10.1136/bmjopen-2022-061051

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-061051).

Received 20 January 2022
Accepted 02 March 2022

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ABSTRACT

Introduction For the growing number of children with in utero and postpartum exposure to HIV and/or antiretrovirals, it is unclear which exposures or risk factors play a significant role in predicting worse neurodevelopmental outcomes. This protocol describes a prospective longitudinal cohort study of infants born to mothers living with HIV and those born to mothers without HIV. We will determine which risk factors are most predictive of child neurodevelopment at 24 months. We aim to create a risk assessment tool to help predict which children are at risk for worse neurodevelopment outcomes.

Methods and analysis This study leverages an existing Kenyan cohort to prospectively enrol 500 children born to mothers living with HIV and 500 to those without HIV (n=1000 total) and follow them from birth to age 24 months. The following factors will be measured every 6 months: infectious morbidity and biological/sociodemographic/psychosocial risk factors. We will compare these factors between the two groups. We will then measure and compare neurodevelopment within children in both groups at 24 months of age using the Child Behaviour Checklist and the Bayley Scales of Infant and Toddler Development, third edition. Finally, we will use generalised linear mixed modelling to quantify associations with neurodevelopment and create a risk assessment tool for children ≤24 months.

Ethics and dissemination The study is approved by the Moi University's Institutional Research and Ethics Committee (IREC/2021/55; Approval #0003892), Kenya's National Commission for Science, Technology and Innovation (NACOSTI, Reference #700244) and Indiana University's Institutional Review Board (IRB Protocol #110990). This study carries minimal risk to the children and their mothers, and all mothers will provide written consent for participation in the study. Results will be disseminated to maternal child health clinics within Uasin Gishu County, Kenya and via papers submitted to peer-reviewed journals and presentation at international conferences.

Strengths and limitations of this study

- Utilises a culturally adapted scale that has been validated within this setting to measure neurodevelopment.
- Well powered to compare neurodevelopment outcomes between children who are HIV-exposed and HIV-unexposed.
- Study setting within the Academic Model Providing Access to Healthcare in Eldoret, Kenya and the East Africa International epidemiology Databases to Evaluate AIDS consortiums, enabling scale-up if tool is found to be effective.
- Limited information on gestational dating of the infant, relying primarily on maternal last menstrual period.
- While measuring a wide array of potential contributors to neurodevelopmental outcomes, it is impossible to measure all possible variables influencing the primary outcome.

INTRODUCTION

Despite gains in access to HIV treatment and prevention, children born to mothers with HIV often do not thrive.[1] Exposure to HIV or antiretrovirals may impact neurodevelopmental outcomes among children who are HIV-exposed but uninfected (HEU). Most of the estimated 14.8 million children who are HEU live in sub-Saharan Africa,[2] accounting for >15% of the general child population in some countries.[3] Children who are HEU face many risk factors for worse neurodevelopmental outcomes, such as malnutrition, poverty, recurrent illness and suboptimal child stimulation.[4–7] These risk factors confound the potential impact of exposure to HIV or antiretrovirals on neurodevelopmental outcomes.[8] The complex interplay between these factors remains largely unexplored, and

the risk of worse neurodevelopmental outcomes in children who are HEU is mostly undefined.

An increasing concern for clinicians, researchers and policymakers is whether HIV or antiretroviral exposures cause neurodevelopmental delays in children born to mothers with HIV.[9 10] While children living with HIV have lower neurocognitive scores compared with children who are HIV-unexposed, uninfected (HUU), the results are inconsistent for children who are HEU.[9 11–17] Brain MRI differences have been detected in children who are HEU, and behavioural differences occur in antiretroviral-treated animal models.[10 14] However, these data were limited by small sample size, inconsistent neurodevelopmental domains impacted and a lack of mechanistic data.[9] Furthermore, mixed outcomes have resulted from clinical assessments of neurodevelopmental performance comparing children who are HEU and HUU.[10 15 17] Without a clear understanding of this issue, over 1 million HEU children born every year[18] might be at risk for neurodevelopmental delays, preventing them from optimising their quality of life, academic achievement and economic potential with the possibility of severe consequences for countries with high HIV prevalence.[8 17]

METHODS AND ANALYSIS

Objectives and aims

The primary objectives of this study are twofold. First, we will evaluate potential risk factors over the first 2 years of life in children who are HEU and HUU and define those associated with worse neurodevelopmental outcomes at 24 months. Then, we will create a risk assessment tool to predict children with worse neurodevelopmental outcomes. The following specific aims will be pursued to achieve these objectives:

- AIM 1: Evaluate potential risk factors for worse neurodevelopmental outcomes in young Kenyan children who are HEU and HUU.
- AIM 2: Compare neurodevelopmental outcomes between children who are HEU and HUU in Kenya at age 24 months.
- AIM 3: Create a risk assessment tool to predict which children are at risk for worse neurodevelopmental outcomes at 24 months.

This study will determine the interconnected factors associated with worse neurodevelopmental outcomes in children who are HEU and HUU in Kenya, including exposure to HIV and antiretrovirals (eg, maternal dolutegravir-based or efavirenz-based therapy) (figure 1). The risk assessment tool will allow clinical providers to institute early childhood interventions for children at risk for worse neurodevelopmental outcomes.

Setting

This study, also known as the Tabiri Study ('Tabiri' translates into the Swahili word 'Predict'), is being conducted within the clinical and research infrastructure of the Academic Model Providing Access to Healthcare (AMPATH) in western Kenya. AMPATH is a collaborative partnership between Moi University, Moi Teaching and Referral Hospital (MTRH) and a consortium of North American universities, led by Indiana University. Located in the city of Eldoret, MTRH is the second-largest national referral hospital in Kenya and headquarters of the AMPATH programme. As a referral hospital, MTRH serves 4 million people throughout the surrounding area. AMPATH is one of the largest HIV programmes in sub-Saharan Africa, with a unique clinical and research infrastructure.[19–21]

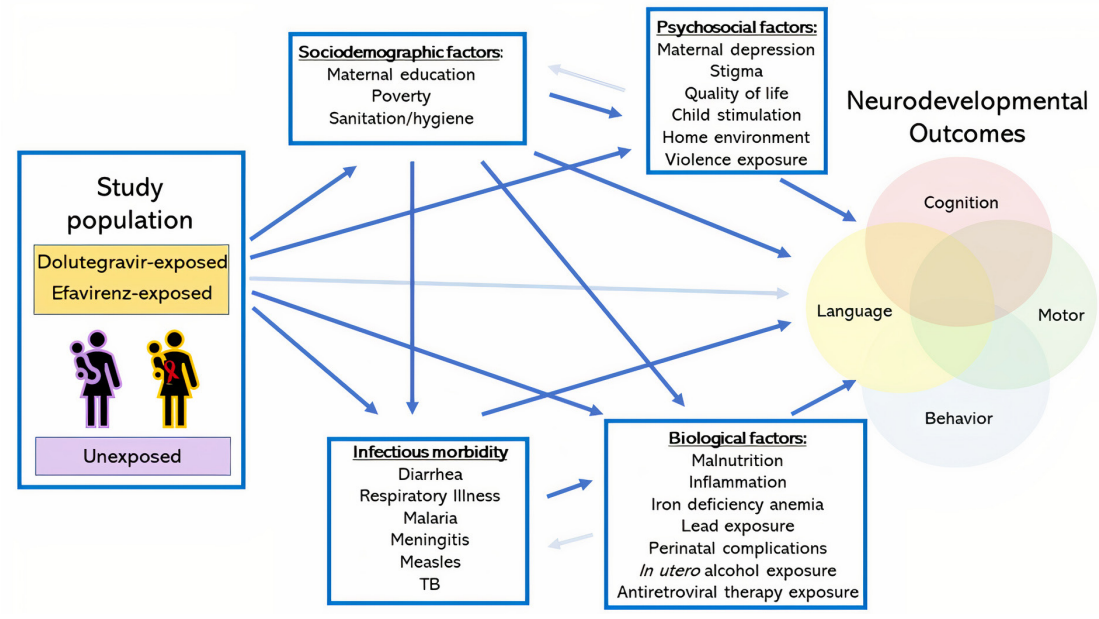

Figure 1 Proposed conceptual model of the risk factors impacting neurodevelopment.

AMPATH is the flagship programme for the East African International epidemiology Databases to Evaluate AIDS Regional Consortium (EA-IeDEA). This study leverages a cohort of 1600 pregnant women within an EA-IeDEA Consortium entitled, 'Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO, clinicaltrials.gov # NCT04405700).' The MANGO study is a pharmacovigilance surveillance programme examining the impact of current era antiretroviral medications on pregnancy outcomes. MANGO is prospectively enrolling 800 pregnant women with HIV, treated with either dolutegravir-based or non-dolutegravir-based regimens and 800 pregnant women without HIV from MTRH and following them until delivery, when birth outcomes and congenital defect data are collected. Additionally, MANGO is undertaking a cross-sectional evaluation of all deliveries at MTRH. MANGO study enrolment commenced in September 2020. The Tabiri study, which commenced in October 2021, is recruiting directly from the MANGO cohorts. We anticipate recruitment will continue until July 2023 and study completion will occur in August 2025.

Eligibility criteria

Aims 1/2

For caregivers, *inclusion criteria* includes: (1) prior research participation in MANGO; (2) diagnosed with HIV before or during current pregnancy OR HIV-uninfected and matched to a woman with HIV; (3) ≥18 years and (4) willing to participate in a longitudinal follow-up study.

All live-born infants born to study participants (ie, those women meeting the above-mentioned inclusion criteria and enrolled) will be included.

For caregivers, *exclusion criteria* include: (1) unable to consent in English or Kiswahili; (2) any condition that would impair the ability to give informed consent; (3) delivered infant >7 months prior to enrolment (first study visit is at 6 months, with a ±1 month grace period) and (4) medical record documentation of death before delivery or transfer to another facility.

For infants, the only exclusion criterion is fetal demise or stillbirth.

Aim 3

For the cognitive interview, inclusion criteria are as follows: (1) caregiver of a child <age 3 years, and (2) ≥18 years. Exclusion criteria include (1) being unable to consent in English or Kiswahili, or (2) having any condition that would impair the ability to give informed consent.

Study design and procedures

The Tabiri study is a prospective longitudinal cohort study (figure 2). Further details about the study design are as follows:

Aim 1

Evaluate potential risk factors for worse neurodevelopmental outcomes in young Kenyan children who are HEU and HUU. *Approach:* leveraging the MANGO study cohort, we will prospectively enrol 500 Kenyan children who are HEU and 500 who are HUU and monitor them from birth to age 24 months. Every 6 months, we will measure: *infectious morbidity* (diarrhoea, pneumonia, malaria, meningitis, tuberculosis and measles), *biological factors* (birth history, alcohol exposure, antiretroviral exposure, anthropometrics, breastfeeding and nutritional history, inflammatory biomarkers, lead exposure, iron deficiency anaemia), *psychosocial factors* (child stimulation, harsh punishment, quality of life, violence exposure and maternal mental health) and *sociodemographic factors* (water/sanitation, poverty and maternal education). The laboratory investigations will occur at age 6 and 24 months and home environment at 18 months.

Aim 2

Compare neurodevelopmental outcomes between 24-month-old children who are HEU and HUU in Kenya. *Approach:* Using the Child Behaviour Checklist (CBCL) and the Bayley Scales of Infant and Toddler Development, third edition (Bayley-3), which our team

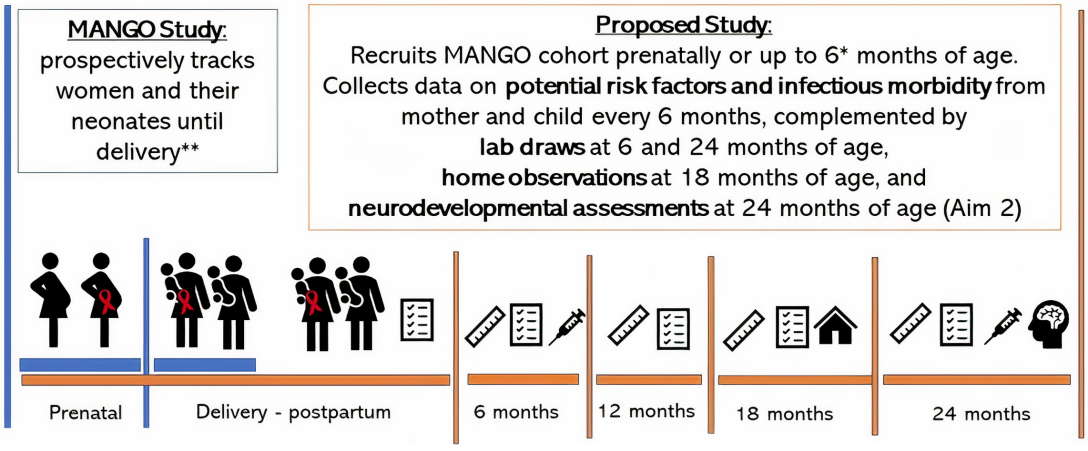

Figure 2 Study activities. *±1 month window to grant for each study visit. **A small subset of children with congenital anomalies within the MANGO cohort are followed beyond delivery.

has culturally adapted and internally validated for use in Kenya, we will measure cognition, language, motor and behaviour domains on participants at age 24 months. We will compare results between children who are HEU and HUU, adjusting for confounding factors, such as infectious morbidity history and biological and social factors. We anticipate that children who are HEU will have worse neurodevelopmental outcomes compared with their HUU peers.

Aim 3

Create a risk assessment tool to predict which children are at risk for worse neurodevelopmental outcomes at 24 months. *Approach:* Using generalised linear mixed models, we will quantify associations among multiple factors with child neurodevelopmental outcomes and create a risk assessment tool for children <age 24 months. We will evaluate this tool's face validity.

Recruitment and consent

For the cohort recruited for aims 1 and 2, written informed consent will be obtained for all participants. Potential participants will be recruited from two different cohorts of the MANGO study: C1 and C2. The C1 cohort consists of pregnant women who are enrolled in the MANGO study during their prenatal visits at MTRH's antenatal clinic, who are then either coenrolled or later contacted for enrolment into the Tabiri Study. The C2 cohort consists of women who have come to MTRH to deliver their babies and their data are recorded into the MANGO database. Within the postpartum period, potential participants will be reviewed for inclusion and approached for study consent after returning to the postpartum ward. Women living with HIV are matched, by age and C1 from which they were recruited, to women not living with HIV.

We reimburse participants 500KSh (approximately US$5) for each study visit. An additional 500ksh are given during visits involving assessments (eg, neurodevelopmental/behaviour assessments, home observations) or laboratory studies, due to additional time required for participation. Refreshments and snacks are available to study participants during their visits.

Some enrolled participants will not remain engaged for the entire duration of follow-up. If participants wish to withdraw from the study, they may do so at any time and without any consequence. However, to encourage retention in the study, we will also compensate study participants who complete 24 months of follow-up with 2000ksh.

For aim 3, 10 caregivers of young children will be recruited by convenience sampling from the MTRH maternal–child health clinic for cognitive interviewing. They will be asked about their interpretation of the items within the risk assessment tool to ensure its face validity. Study activities will take approximately 1–2 hours and we will compensate study participants 500ksh for their time and travel. Written informed consent will be obtained.

Data collection for biological risk factors

Prenatal history, birth outcomes and in utero exposures

After enrolment, data from the MANGO database will be pulled and evaluated continuously and dichotomised when clinically relevant categories exist: weeks of gestation, maternal anaemia, birth weight, APGAR scores and reported infections during pregnancy. We will also extract data regarding maternal HIV viral load testing, initiation of antiretrovirals during pregnancy and antiretroviral regimen categorisation for our data analysis. AMPATH Medical Record System data on postpartum infant antiretroviral prophylaxis regimen will also be collected. At baseline, questions will be asked about maternal alcohol use during pregnancy using the WHO eight-question survey.[22]

Laboratory testing

At ages 6 and 24 months, children will undergo phlebotomy. A complete blood count and ferritin will be performed to evaluate for iron deficiency anaemia under the WHO guidelines at[23 24] ferritin 12 µg/L and haemoglobin <10.5 mg/L. Blood lead level will be measured, with ≥5 µg/dL considered elevated. The following inflammatory biomarkers will be measured in cryopreserved plasma samples: CRP, fibrinogen, D-dimer, sCD163, sCD14, IL-2R, IFNα, IFNγ, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12 p70, IL-15, IL-17A, IL-21, IL-22, TWEAK, Tau and TNFα. For breastfeeding children who are HEU, plasma samples will be sent to Indiana University and tested using liquid chromatography tandem mass spectrometry (LC-MS/MS) methods to quantify dolutegravir[25] and efavirenz levels and their respective metabolites.

Anthropometrics, breastfeeding, and nutritional diversity

Weight, height, occipitofrontal circumference and reported breastfeeding frequency and duration will be measured at baseline, 6, 12, 18 and 24 months. Nutritional diversity is measured using the minimum dietary diversity scale designed by the WHO.[26]

Infectious morbidity

If a child is hospitalised, the INFORM Infectious Morbidity Case Report Forms will be completed. These forms will capture a spectrum of infectious morbidity data, including diarrhoea, pneumonia, malaria, meningitis, measles and tuberculosis. These forms have been designed to characterise the type of infectious event for which a child is hospitalised, attribute the degree of certainty for each diagnosis and assign illness severity. Families will be asked to contact the study team if the child requires hospitalisation. The study team will maintain monthly phone contact with study participants to inquire about hospitalisation status.

Additionally, we will collect data on the vaccination and HIV status of all children from medical records after the anticipated HIV testing visits. A future amendment will add the ability for HIV testing for participants and their mothers (who previously tested negative) at 24 months.

Social risk factors

At baseline enrolment and every six months, social factors will be evaluated in all study participants. The following domains will be assessed: child stimulation and harsh punishment (using questions adapted from the UNICEF multiple indicator cluster surveys),[27] HIV-related stigma (using the NIH Stigma Scale);[28] violence exposure (using Traumatic Event Screening Inventory-Parent Report Revised)[29 30] and maternal depression (Patient Health Questionnaire-9).[31 32] To optimise time during study visits, we will only assess the following at baseline: maternal education, sanitation-hygiene-water quality (UNICEF/WHO Core Questions on Water, Sanitation, Hygiene),[33] maternal alcohol consumption during pregnancy (measured using the WHO 8-question survey)[22] and poverty risk (Poverty Probability Index).[34] Follow-up questions will be targeted to items that may have changed from the prior evaluation. Quality of life (Paediatric Quality of Life Inventory)[35] will be measured at 24 months, the earliest age for which this measure is validated. Home Observations for Measurement of the Environment (HOME)[36] evaluations will be performed at 18 months within the participants' homes to evaluate child stimulation and environment, as this is an ideal time for observations of recent maternal–child interactions.

Primary outcomes (measured at 24 months)

The Bayley Scales of Infant and Toddler Development, third edition (Bayley-3)

Bayley-3 is an international standardised assessment used to evaluate neurodevelopmental outcomes in research settings.[9 37] The following domains will be measured within the proposed study: cognition, receptive language, expressive language, fine motor and gross motor, with administration taking 45–60 min. This version was previously culturally modified within this population.[38]

We will be comparing the mean raw scores for each domain of the Bayley-3 and dichotomising the proportion of children as having 'adverse neurodevelopmental outcomes', as defined by the presence of either a low score (lower than two SD below the mean) or failed completion after two attempts.

Child Behaviour Checklist /1.5–5 years (CBCL)

CBCL is an international assessment of internalising, externalising and total behaviour problems.[19] It has been translated into Kiswahili and culturally adapted for contextually relevance in Kenya.[39] This caregiver-reported measure will be done at 24 months and will take 30–45 min to administer. The mean difference in raw scores will be used for total, internalising and externalising behaviours and a raw score of <2 SD below the total sample mean will be considered as having worse neurodevelopmental outcomes.

Quality monitoring

All assessors administering the Bayley-3 must undergo training, be approved by a clinical psychologist for independent administration and have >6 months of practical experience. All assessors administering the CBCL will participate in a full-day workshop on administering and scoring the CBCL, including didactics, one-on-one coaching and practice with simulated patients. All assessors will be blinded to the HIV status of the child. To maintain quality, all administrations will be video-recorded. Each week, the study coordinator will lead the team of Bayley-3 -trained research assistants in reviewing at least 5% of the videos to optimise quality, consistency and accuracy of assessments. A monthly team call will focus solely on the quality of administration of the Bayley-3 and CBCL. During these calls, the team will troubleshoot issues that may have been encountered during testing administrations and review video-recordings and scoring sheets.

Every six months, eight children will be randomly selected for repeat Bayley-3 testing that will occur the same day as their initial evaluation. This repeat testing will aid in our quality monitoring. Test–retest and inter-rater reliability will be assessed on the Bayley-3 in these children using an intraclass correlation coefficient (ICC) for absolute agreement, with occasions and raters specified as random effects. Inter-rater reliability will be determined by repeating the tests with different assessors on the same child after a substantial break in the day. For intra-rater reliability, short sections of the test will be repeated by the same assessor on the same child later in the day during training to ensure consistency. An ICC of ≥0.8 will be considered strong reliability; if ICCs are below <0.8, we will retrain assessors to ensure their adherence to proper administrations.

Sample size

The proposed study is powered for the primary outcome of determining whether, differences in neurodevelopmental outcomes exist between children who are HEU and HUU. Within the neurodevelopment literature, language domains are commonly cited as the domain most consistently impacted on the Bayley-3 in children who are HEU,[40] although a statistically significant difference is not always present.[15] Using data from our pilot study of children who were HEU (n=74) and HUU (n=74), a potential difference existed between these groups in the language domain.[41] While the difference was not statistically significant, these data were helpful for estimating our proposed sample size. Using the Bayley-3 language composite scores of this study, children who were HEU had a mean score of 73.4 (SD 13.7) and children who were HUU had a mean score of 76.3 (SD 12.7).[41] Using an average SD of 13.2, the resulting effect size is 0.22 standardised difference between means (ie, Cohen's d) for continuous neurodevelopment outcomes. With a 0.22 effect size, an alpha of 0.05 and 80% power, the estimated sample size needed is 326 per group. Specifically, the sample size of 326 per HEU and HUU groups will provide 80% power to detect a small effect size of 0.22 (Cohen's d) for continuous risk variables, and 80% to

detect an absolute difference in categorical risk factors of 6% (eg, 5% vs 11%; OR=2.33) or 11% (eg, 50% vs 61%, OR=1.55) depending on the risk factor prevalence. We assume lost-to-follow-up rates will be 25%–30% between enrolment at 24 months, so our goal will be to recruit 500 per group, total n=1000. This cross-sectional-based power calculation is conservative. The actual analyses for aim 1 will have greater power because models will incorporate repeated longitudinal measures for several risk factors, when available.

Patient and public involvement

Our collaborative international research group has performed research in Kenya for over a decade. Prior studies, many involving the local community, informed the study design and consent process for this study.[42–45] At study completion, we will hold a series of meetings among healthcare providers caring for the recruited population (those who work within the MTRH antenatal and postnatal clinics and wards), as well as local village elders and chiefs. During these meetings, we will disseminate the results of the study. We will also ask them what the best method of disseminating the results to the community would be and if feasible, we will proceed to disseminate the information as requested.

Statistical analysis

Aim 1

Our primary analysis will compare potential risk factors for worse neurodevelopment outcomes and infectious morbidity between children who are HEU and HUU. The primary risk factors of interest are biological, psychosocial and infectious morbidity, which will serve as mediators for worse neurodevelopment in the conceptual model (figure 1). In addition, we will include sociodemographic risk factors to adjust for potentially confounding effects. A generalised linear mixed model will be used to compare HEU and HUU on repeatedly measured risk factors. The linear and logit link will be used for continuous and dichotomous risk factors, respectively. The tests of interest will be the main effect of the group indicator (HEU vs HUU), the time effect and the interaction between group and time. The time effect will inform whether risk factors change over time for both groups. The group-by-time interaction effect will inform whether the group difference on risk factors becomes smaller, larger or stays about the same over time. There are multiple theoretically important variables that may differ between children who are HEU and HUU. Therefore, no single variable is identified as the primary-dependent variable for this analysis. However, we will adjust for multiple comparisons with the false discovery rate method at an overall rate of 0.05.[46] Of note, if more than 5% of the children who are HEU are ultimately found to become HIV+, we will include them as a subgroup within these and subsequent analyses.

Aim 2

A generalised linear model will be used, adjusting for sociodemographic, risk factors and other potentially confounding mediators and covariates. All primary and most secondary-dependent variables are continuous and will be modelled with an identity link function. The secondary outcome of dichotomised adverse neurodevelopment will be modelled with a logit link function. A separate model will be performed for each neurodevelopment outcome. The relevant measurements for the covariates for this analysis will be either the cross-sectional at the 24-month time-point or a historical summary variable derived from baseline and/or longitudinal measures.

Aim 3

A generalised linear mixed model will be used to develop the risk assessment tool. The logit link function will be used because the outcome will be dichotomously scored (worse vs not-worse neurodevelopment). We will explore modelling neurodevelopment scores as continuous outcomes with the linear mixed effects models. The following independent variables will be entered in the model as time-varying covariates within the following categories: infectious morbidity, biological risk factors and social risk factors, while adjusting for sociodemographic risk factors. The group variable (HEU vs HUU) will also be included as a predictor. Inflammatory markers and infant plasma antiretroviral therapy levels will be excluded from analysis due to the challenges of performing them sustainably within a clinical setting. The tests of interest will be the main effect for each predictor: the time effect, the interactions between risk factors and the interactions between group and time. The OR and 95% CI will be reported for each risk factor. The use of longitudinal measurements will allow us to determine whether the initial measurement of each risk factor contains enough information to predict worse neurodevelopment, or whether the accumulation of repeated measurements for particular risk factors is needed. The test of the interaction between risk factors and time will be used to determine whether the strength of the association changes over time. A significant interaction will be followed by use of the model's coefficients to determine the precise time point when the risk factor becomes a stronger predictor. The use of repeated measures of the risk factors provides a more robust estimate of the main effect for each risk factor.

Additions and clarifications of original protocol to current protocol

Some study activities noted above are updates from the original protocol. One update was outlined within the original protocol as a potential solution for low recruitment. Originally, the study stated that only MANGO C1 cohort would be recruited when the infants were 2 weeks of life or older. However, due to delays in enrolment and other logistical challenges, both the C1 and C2 cohorts are now eligible for recruitment. Additionally, an approved amendment allowed us to recruit 10 individuals

for cognitive interviewing prior to recruitment for aims 1 and 2. This was necessary to help ensure that the wording and translations of study forms were accurate and understood well by local participants. These forms had not previously been used by our study team before and included the Traumatic Events Screening Form, the Peds-Quality of Life Questionnaire and the WHO's 8 question survey. These interviews were completed prior to data collection, optimising the functionality of the forms. Finally, we added questions focused on each infant's first 28 days of life to better understand neonatal morbidity for this study cohort, as children who are HEU were recently found to have higher morbidity when hospitalised within the neonatal period compared with their HUU peers in South Africa.[47]

Planned changes include additional questions related to volume of cow's milk consumption, developmental screening questions administered at each of the 6-month study visits and additional HIV testing for all infants and mothers who were recruited within the HIV-uninfected cohort at 24 months. We anticipate these changes will be approved and implemented in mid-2022.

ETHICS AND DISSEMINATION

The study is approved by the Moi University's Institutional Research and Ethics Committee (IREC/2021/55; Approval #0003892), Kenya's National Commission for Science, Technology and Innovation (NACOSTI, Reference #700244) and Indiana University's Institutional Review Board (IRB Protocol #110990). This study carries minimal risk to the children and their mothers, and all mothers will provide written consent for participation in the Tabiri study. Assent will not be obtained due to the young age of the children. Results will be disseminated to maternal child health clinics within Uasin Gishu County, Kenya and via papers submitted to peer-reviewed journals and presentation at international conferences.

A critical goal of the risk assessment tool is to identify children at risk for not meeting their full developmental potential early so that interventions may be initiated during critical periods to create a strong foundation for learning in the future. While some risk factors may be directly intervened on (eg, providing a nutritional referral for malnourished children or physical therapy when motor delay is present), others are not easily modifiable (eg, low maternal education). In these instances, caregivers will be given materials used within a prior nurturing care intervention, which were deemed acceptable and useful in improving child–parent relationships.

At study completion, we will hold a series of meetings among healthcare providers caring for the recruited population, local village elders and chiefs.

We also anticipate this study will yield outcomes that may be presented within at least three presentations at national/international meetings. With our strong collaboration with IeDEA, we are well positioned to evaluate the effectiveness and implementation of this tool globally.

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Acknowledgements We would like to acknowledge the support of faculty and staff at Moi University, Indiana University, MTRH and AMPATH for supporting this study, by providing insights and ensuring that the research we set out to accomplish will work towards improving the lives of children living in western Kenya. We would also like to thank, in advance, the mothers and infants who were willing to engage in this longitudinal study, shouldering this inconvenience so that we can gain knowledge to help improve care for children globally. We would also like to thank Melissa Thomas for her careful review and editing of the manuscript.

Contributors EO assisted with study conceptualisation, subject enrolment, data collection, analysis and protocol writing. He is the site-PI for this study. OEK assisted with initial protocol manuscript writing and editing. RV and WN assisted with study conceptualisation and protocol writings and will lead the data collection and analysis related to the risk assessment tool. POM assisted with study conceptualisation, statistical analysis and protocol writing. WT assisted with study conceptualisation and statistical analysis. AK assisted protocol writing and will lead the laboratory testing in Kenya and protocol writing. ZD assisted with study conceptualisation and will assist with laboratory testing in USA. ALS assisted with study conceptualisation and protocol writings and will lead the data collection and analysis related to infectious morbidity. JMH, EW and RCP assisted with study conceptualisation, MANGO subject enrolment, data collection, analysis and protocol writing. JGC assisted with study conceptualisation, MANGO subject enrolment, data collection, analysis and manuscript writing. KW-K provided overall oversight throughout the MANGO project, including study conceptualisation, enrolment, data collection, analysis and protocol writing. MSM assisted with study conceptualisation and protocol writing and will lead all aspects of the study, including subject enrolment, data collection, analysis and manuscript writing.

Funding This work was supported by the National Institutes of Health (NIH) Grant #R01HD104552. Dr MSM is the Principal Investigator (PI) and EO as the Site PI. The overall 'Measuring Adverse Pregnancy and Newborn Congenital Outcomes' MANGO study, from which this study is recruiting, is funded by the NIH Grant # U01AI069911. The title of the overall grant is 'East Africa International Epidemiology Databases to Evaluate AIDS (EA-IeDEA) Regional Consortium'.

Competing interests None declared.

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

Patient consent for publication Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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