



CONCEPT SHEET: MULTIREGIONAL ANALYSIS

Date of EC approval:	<i>(to be added by UCT data centre)</i>
Tracking number:	<i>(to be added by UCT data centre after EC approval)</i>
Title:	Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO): An leDEA Collaboration Study
Concept Lead: Email:	Rena Patel (rcpatel@uw.edu); John Humphrey (humphrjm@iu.edu)
Collaborators:	<i>leDEA-Southern Africa:</i> Emma Kalk, Ushma Mehta, Mary-Ann Davies <i>leDEA-East Africa:</i> Edwin Were, Beverly Musick, Constantin Yiannoutsos, Kara Wools-Kaloustian
leDEA Correspondent: Email:	Rena Patel (rcpatel@uw.edu); John Humphrey (humphrjm@iu.edu)
Data Manager: Email:	Beverly Musick bsmusick@iu.edu
Lead Statistician: Email:	Constantin Yiannoutsos cyiannou@iu.edu
Where will data be merged?	Indiana University
Where will statistical analyses be done?	Indiana University
Abstract: (±200 words)	Background: Few HIV treatment programs routinely collect and monitor reproductive health outcomes, especially for pregnancy and birth outcomes. Surveillance systems that are ready and responsive to future reproductive health issues arising from antiretroviral treatment (ART), for instance, need be urgently established within large HIV treatment programs. Objective: To enhance and test a multiregional infrastructure to conduct

	<p>pharmacovigilance (PV) among pregnant women living with HIV on ART within the International Epidemiologic Databases to Evaluate (leDEA) consortium.</p> <p>Methods: We will use a retrospective and prospective cohort design to enhance existing data infrastructures at two pilot HIV treatment programs, with two sites each at AMPATH, Kenya and CIDER, South Africa. We will conduct a proof-of-concept analysis with this dataset to examine any associations between ART and (a) pregnancy and (b) infant/birth outcomes. After initial piloting of the protocol at sites in South Africa and Kenya, we would like to consider duplication of the protocol at one or more sites each in the Central and West Africa leDEA regions.</p> <p>Anticipated Results: This study will establish PV infrastructure within leDEA that can be scaled within the broader leDEA network.</p>
<p>Project outline: (±1000 words)</p>	<p>Background</p> <p>In May 2018, researchers from Botswana reported on a potential increased risk for infant neural tube defects among women living with HIV and exposed to dolutegravir (DTG)-containing antiretroviral treatment (ART) around the time of conception (1). This report led to HIV treatment programs, worldwide, scrambling for data on pregnancy outcomes. The across-the-board conclusion was that the current prevention of mother-to-child transmission (PMTCT) data capture tools are inadequate to address the need for more data on the impact of antiretrovirals on birth outcomes, including congenital abnormalities. Few HIV programs routinely collect and monitor reproductive health outcomes, especially during pregnancy. The limited data that does exist often has conflicting findings (2). Nonetheless, it is essential for HIV treatment programs in resource-limited settings to institute robust monitoring tools for reproductive health outcomes. Mass HIV treatment programs result in <i>in-utero</i> exposures at scale, and invariably newer antiretrovirals with poorly understood safety profiles in pregnancy will become available for both HIV treatment and prevention. Therefore, surveillance systems that are ready and responsive to future issues arising from existing and future antiretrovirals need be urgently established within large HIV treatment programs globally. Such surveillance systems can also be leveraged to fill knowledge gaps regarding other therapeutic exposures during pregnancy—i.e. a broader pharmacovigilance (PV) infrastructure for pregnancy and birth outcomes.</p> <p>Objectives and hypotheses</p> <p>The objective of this study is to establish a multiregional infrastructure for adverse pregnancy and birth outcomes surveillance in resource-limited settings.</p> <p>Aim 1: To create standardized protocols and data exchange standards within leDEA. We will leverage the existing leDEA Data Exchange Standard (DES) to create a Data Standards Task Force and Data Coordinating Center for adverse pregnancy and birth outcomes surveillance, adding new tables and expanding existing ones to include new concepts and fields responsive to the needs of the study.</p>

Aim 2: To enhance existing infrastructures for data collection, linkage, and management of observational data at two pilot HIV treatment programs in the Southern Africa and East Africa leDEA regions. We will utilize a multi-layered strategy that includes 1) training of facility workers to detect congenital abnormalities in infants, 2) cross-sectional, patient-level data collection on pregnancy exposures and birth outcomes, 3) prospective enrollment of infants for photographs of congenital abnormalities and expert review, and 4) prospective enrollment of HIV+ and HIV- pregnant women who enroll in antenatal care at the site but deliver outside the site.

Aim 3: Compare pregnancy and birth outcomes between HIV+ and HIV- women, and between HIV+ women exposed to different ART regimens (including DTG-based regimens). Hypothesis: HIV infection and ART increase the risk for adverse pregnancy and perinatal outcomes (e.g. stillbirth, preterm delivery, small-for-gestational-age) compared to HIV- women, but there will not be a significant association between HIV status or ART exposure and the incidence of congenital abnormalities compared to HIV- women.

Study design

Design: Cohort study with cross-sectional and prospective components.

Study sites: Two sites each affiliated with the Centre for Infectious Disease Epidemiology and Research (CIDER) in South Africa and the Academic Model Providing Access to Healthcare (AMPATH) in Kenya.

Study population: 1) All pregnant women (any age; HIV+ and HIV-) with a documented birth outcome at a study site; 2) all infants/stillbirths delivered at the site with suspected congenital abnormalities identified by surface exam; 3) HIV+ and HIV- women who enroll in antenatal care at the site but do not deliver at the site.

Eligibility criteria

All sites:

- a. Adverse pregnancy and birth outcomes: All deliveries and pregnancy losses at the study sites will be included in the study, regardless of whether or where women previously received antenatal care.
- b. Clinical photographs of infants with suspected congenital abnormalities: Mothers of all infants with suspected congenital abnormalities (based on surface exam by facility staff) will be approached to consent for photographs of the abnormalities. Women who have a birth outcome occurring at < 24 weeks gestation will be excluded given that in Kenya and South Africa, non-live births < 24 weeks gestation are considered miscarriages rather than stillbirths.

AMPATH, Kenya only:

- c. Field outreach for non-site deliveries: All HIV+ pregnant women and a 1:1 random sample of HIV- pregnant women enrolling in antenatal clinic at the site will be approached in the antenatal clinic to consent for phone contact and field outreach. In order to ascertain the pregnancy and birth outcomes for these women, outreach will be performed if

they do not deliver at the site within two weeks following the estimated date of delivery.

Key variables and definitions

- a. Pregnancy: clinic name, estimated date of delivery, gravidity/parity, history of prior stillbirths or neonatal deaths, history of other children with congenital abnormalities, current gestation (single, multiple), antenatal care visit dates, documented medical comorbidities (e.g. diabetes, hypertension, heart disease, seizure disorder), medications during conception/pregnancy (including folate and vitamin supplements, anti-tuberculosis drugs), substance use (e.g. tobacco, alcohol, illicit drug), height/weight (prior and during pregnancy), laboratory results (e.g. hemoglobin, RPR, HIV testing), ultrasound results (if performed).
- b. Delivery: delivery site (facility name, home, other), mode of delivery (spontaneous vaginal delivery, elective c-section, emergency c-section), date of delivery, intrapartum antiretroviral prophylaxis and dates.
- c. HIV and OIs (women): ART regimen during conception/pregnancy and dates, viral loads during pregnancy and dates measured, CD4 counts and WHO stages at ART initiation and during pregnancy, on anti-tuberculosis drugs during pregnancy.
- d. Infant/stillbirth: sex, APGAR score (1, 5 min), birth weight/length/head circumference, estimated gestational age at birth, neonatal outcome after delivery (Discharged, Referred, Stillborn, Died after Birth, Admitted), feeding on discharge (Exclusive Breast Feeding, Exclusive Formula Feeding, Unable to Ascertain), descriptions of congenital abnormalities on surface exam (e.g., extra digit, hydrocephalus, skull defects, eyes, face, mouth/lip/palate, chest, abdomen, anus, limbs, spine (including neural tube defects), hips, genitalia, skin, etc.).

Outcomes

- a. Pregnancy outcomes: Live Birth, Still Birth, Miscarriage, Termination of pregnancy, Ectopic Pregnancy, Molar Pregnancy, Not Pregnant; subcategories of live birth/still birth include term (≥ 37 weeks gestation), pre-term (32-37 weeks), very pre-term delivery (<32 weeks).
- b. Infant/birth outcomes: structural congenital abnormalities on surface exam, classified by WHO criteria by severity (i.e. major and minor) and within predefined systems (e.g., central nervous system [hydrocephalus, microcephaly, neural tube defect], gastrointestinal [anorectal malformation, imperforate anus], limb [absent radius, polydactyly], skull, eyes, face, mouth/lip/palate, chest, etc; also includes low birth weight (<2500 g), small for gestational age (<10th percentile) or very small for gestational age (<3rd percentile) according to WHO criteria (these outcomes are not mutually exclusive)

Study procedures, data collection and statistical methods

In-service training on surface examination and adverse drug event reporting: The surveillance program at all sites will rely on routinely collected clinical data and newborn surface examination by nursing staff

together with the study team. This structure promotes the sustainability of the project but requires that the staff are well trained to collect reliable data and correctly classify birth outcomes and congenital abnormalities. The study teams will conduct training sessions with clinical and clerical staff in complete and accurate documentation and surface examination. Standardized WHO training materials (e.g. newborn exam, atlas of congenital anomalies) will be used in these training sessions, with additional training provided during the study (3, 4).

Data collection:

(1) CIDER, South Africa: CIDER initiated the “B positive” project in 2016 which has overseen the establishment of a Pregnancy Exposure Registry (PER) and birth defect surveillance (BDS) system at two sentinel sites in the Western Cape: Gugulethu Midwife Obstetric Unit and Mowbray Maternity Hospital. The PER/BDS is an electronic system designed to collect data on pregnancy exposures (e.g. medications, traditional medicines, alcohol, tobacco products and illicit drugs) during routine care, leveraging an already established provincial electronic medical record system. All deliveries and pregnancy-losses at each site be included in the BDS. Exposure data will be collected retrospectively from the maternal case record; data clerks based at the delivery sites will collect birth data from maternal case records. Additionally, for all infants ≥ 24 weeks gestation (alive or stillborn) with suspected congenital abnormalities on surface exam, clinical photographs will be taken to confirm and classify these abnormalities. The photographs will be reviewed on an ongoing basis by an expert in genetics/teratology.

(2) AMPATH, Kenya: Data clerks stationed on the maternity wards at Moi Teaching and Referral Hospital and one other site (TBD) will be responsible for entering data from maternal case records cross-sectionally for all women and their infants delivered at the site, using tablet-based REDCap instruments. Clinical photographs of infants with suspected congenital abnormalities and expert review will occur similar to the S. Africa protocol. Additionally, unlike the Western Cape in South Africa where the vast majority of women deliver at a health facility, in western Kenya approximately a third of women deliver at home rather than in a health facility, which includes approximately 25-43% of women who enroll in antenatal care (5). To mitigate bias, all HIV+ pregnant women and a 1:1 random sample of HIV- pregnant women enrolling in antenatal clinic at the site will be approached in the antenatal clinic to consent for phone contact and field outreach to ascertain the pregnancy and birth outcomes if they do not deliver at the site.

(3) Additional Sites in Central and West Africa: Data collection will be adapted to the existing infrastructure at the sites but will likely mirror that outlined under AMPATH, Kenya above.

Statistical analysis: We will describe the risk for each type of congenital anomaly by the exposure groups, reporting our findings with incidence rates (events per 1000 deliveries) and rate ratios (i.e., similar to the Tsepamo study in Botswana). The primary outcome will be the incidence of all congenital anomalies in infants born to HIV+ and HIV- women, with

secondary outcomes considering the risk of neural tube defects specifically and additional outcomes listed above, according to ART exposure regimen and timing (i.e. at conception or later during pregnancy). We will use univariate and multivariate Poisson regression models, adjusting for repeated measures for the same woman. Covariates we will consider adjusting for include demographic, clinical and site-level factors, and region.

Sample size considerations

The county HIV prevalence among women 15-49 years, annual deliveries volumes and HIV+ deliveries at each site are listed in Table 1.

Table 1. CIDER and AMPATH sites, county HIV prevalence among women 15-49 years, and annual patient volumes.

Study site	County HIV prevalence	Total Deliveries	Total HIV+ Deliveries
CIDER, South Africa			
Gugulethu Midwife Obstetric Unit	30%	2,500	750
Mowbray Maternity Hospital	18%	10,500	1,890
AMPATH, Kenya			
Moi Teaching and Referral Hospital	5.5%	12,300	677
Site #2 (e.g. Busia County Hospital)	9.4%	4,000	376
Total	--	29,300	3,693

If, for example, we assume the rate of neural tube defects in the DTG-exposed group is 0.9% and the non-DTG group is 0.1% (based on initial Tsepamo data from Botswana), assuming a two-sided alpha of 0.05, to reach a power of 80%, 529 observations would be required in the DTG group and 2,645 observations would be required in the non-DTG or HIV uninfected groups each (which is a 1:5 ratio for DTG to non-DTG/HIV uninfected observations) (6). Given that the approximations involved in the sample size calculations are based on very low proportions, we performed a simulation study without these approximations, and find that a sample size of 560 observations in the DTG group and 2,800 observations in the non-DTG group will provide adequate power. Given the inclusion of all congenital anomalies for this analysis, we will have >80% power to detect a significant difference between the DTG and non-DTG/HIV uninfected groups, assuming we are able to observe approximately 560 pregnancies in the DTG and 2,800 pregnancies in the non-DTG-exposed groups.

With the successful implementation of this project, leDEA will have developed one of the largest surveillance programs for adverse pregnancy and birth outcomes in resource-limited settings. This will become an invaluable tool in the global HIV response, poised for scale within the broader leDEA network.

References

1. WHO. Statement on dolutegravir: Potential safety issue affecting women living with HIV using dolutegravir at the time of conception. Geneva, Switzerland: World Health Organization (WHO); May 18, 2018.
2. Hill A, Clayden P, Thorne C, Christie R, Zash R. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a

	<p>systematic review. J Virus Erad. 2018;4(2):66-71.</p> <p>3. WHO. Birth defects surveillance training: facilitator's guide. Geneva; 2015.</p> <p>4. WHO. Birth defects surveillance: atlas of selected congenital anomalies. Geneva; 2014.</p> <p>5. Statistics. KNBo. Kenya Demographic and Health Survey 2014 Nairobi; 2014.</p> <p>6. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. The New England journal of medicine. 2018;379(10):979-81.</p>
Ethics:	<p><input type="checkbox"/> This concept uses only the leDEA standard dataset and is covered by the core leDEA ethics approvals.</p> <p>X This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the leDEA standard dataset. Additional ethics approval is required.</p> <p><input type="checkbox"/> This concept does not fall into either ethics category above.</p> <p><i>Describe:</i></p>
Dataset:	<p>X This concept requires new patient-level datasets.</p> <p><input type="checkbox"/> This concept uses existing patient-level datasets submitted for a previous concept: <i>Concept title:</i> <i>Concept number:</i> MR_____</p> <p><input type="checkbox"/> This concept uses leDEA Site Assessment or other leDEA survey data.</p> <p><input type="checkbox"/> This concept does not use any leDEA data (e.g., viewpoint paper).</p>
Target journal(s):	JIAS, AIDS, JAIDS, Lancet Infectious Diseases
Milestones:	<p>Circulation of concept sheet: <October 9, 2019></p> <p>Circulation of draft paper: <date></p> <p>Submission to target journal: <date></p>

Next Steps

Thank you for preparing a concept proposal for an leDEA Multiregional Analysis. All leDEA Concept Sheets are reviewed by the leDEA Executive Committee (EC). Here are the steps for submitting your concept:

1. Before submitting the concept sheet, please **ensure all sections have been completed** or marked not applicable, the document is clean (all edits and comments are removed), and references have been added. If you are participating in an leDEA region, ensure your Regional Principal Investigator has reviewed and approved the concept prior to submission.
2. Concepts that are developed within or have relevance to one or more leDEA Working Groups (see list of Working Groups [here](#)) may be required to **obtain approval from the relevant leDEA Working**

leDEA Multiregional Concept Template 7 May 2018

Groups before submission to the EC. Please contact Aimee Freeman (afreeman@jhu.edu) with questions on this requirement and to circulate the document to the appropriate Working Group.

3. Once the document is ready for circulation to the leDEA Executive Committee, you can **upload it to the leDEA Hub for EC review** at the following link:

<http://bit.ly/iedeasubmit>

The concept will be reviewed by leDEA Administrators prior to circulation to the Executive Committee. If you have questions about the form content, contact Aimee Freeman. For questions about the leDEA Hub upload process, contact the Harmonist team at harmonist@vanderbilt.edu.