Study Title: **Long term outcomes of therapy in women initiated on lifelong ART because of pregnancy in AR Congo**

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Long term outcomes of therapy in women initiated on lifelong ART because of pregnancy in DR Congo

Summary
The US President's Emergency Plan for AIDS Relief (PEPFAR) goal of an AIDS-free generation, re-emphasized in PEPFAR 3.0, will not be achieved without substantial improvement in the adherence to the HIV care continuum among women in maternal and child health clinics (MCH) in resource-limited settings. In a recent meta-analysis of loss to follow-up (LTFU) across the prevention of mother-to-child transmission of HIV (PMTCT) cascade, about 50% of HIV+ pregnant women are already LTFU by delivery; within 3 months of delivery 33.9% of mother-infant pairs are also LTFU. Consequently, half of pediatric infections are currently estimated to occur in the postpartum period during breastfeeding and fewer than 40% of HEI are tested for HIV at 2-3 months. Determinants of this poor performance occur at multiple levels: healthcare delivery systems, providers, and beneficiaries (HIV-infected mothers). Current evidence suggest that beyond individual-level factors, healthcare delivery system level factors are paramount. Quality Improvement (QI) Collaborative is one of the most popular methods for organizing sustained improvement efforts at hospitals and ambulatory practices worldwide. In the Breakthrough Series approach also refer to as continuous quality improvement (CQI),[10] QI teams from multiple sites across a region or country are brought together to focus on a common problem. Over one or two years, experts in clinical and performance improvement provide the group with periodic instructions and encourage the teams to share lessons learned and best practices. However, despite its popularity, CQI effectiveness has never been demonstrated in a randomized trial or a well-designed comparative study. The aims of the proposed study are: 1) to evaluate the effectiveness of CQI interventions in improving long-term retention in care and virological suppression in women who start lifelong ART in MCH clinics and 2) to identify modifiable health delivery system factors associated with retention in care and sustained virological suppression in women who start lifelong ART in MCH clinics. The study will be implemented in Kinshasa, Democratic Republic of Congo (DRC). We will conduct a cluster-randomized trial with health districts as the randomization unit. MCH clinics in the intervention group, will undergo CQI initiatives using participatory data-driven approaches and on-site monitoring and supervisory support. We will use surveys of health facilities, including selected staff, and service beneficiaries (HIV infected mothers) to collect data on key characteristics of the service delivery's organization and providers' and patients' perspective of the HIV care delivery performance. The main outcomes will be LTFU/retention in care, virological suppression, and MTCT rates evaluated at 24 months postpartum.

I. Objectives

The study has two specific objectives:

1- **To identify modifiable health delivery system factors associated with retention in care and sustained virological suppression in HIV-infected women in MCH clinics.** We will use surveys of health facilities, including selected staff, and service beneficiaries (HIV infected mothers) to collect data on key characteristics of the service delivery's organization and providers' and patients' perspective of the HIV care delivery performance. Proportional odds models will be used to identify key modifiable characteristics associated with the main outcomes (LTFU, virological suppression, and MTCT rate).

2- **Evaluate the effectiveness of CQI interventions in improving long-term retention in care and virological suppression in HIV-infected women in MCH clinics.** We will conduct a cluster-randomized trial with health districts as the randomization unit. MCH clinics in the

intervention group, will undergo quality improvement initiatives using participatory data-driven approaches and on-site monitoring and supervisory support.

II. Background and Rationale

Achieving the US President's Emergency Plan for AIDS Relief (PEPFAR) goal of an AIDS-free generation has been re-emphasized in PEPFAR 3.0[1]. The current recommendations of triple antiretroviral therapy (ART) for all HIV-positive pregnant and breastfeeding women regardless of CD4 count (Option B+)[2] requires that, beginning with the first antenatal care visit, HIV-infected mothers strictly adhere to a continuum of care known as the "prevention of mother-to-child transmission of HIV (PMTCT) cascade". The PMTCT cascade includes attendance to regular clinic visits (at a minimum for ART refills), delivery in a health facility, and testing of the HIV-exposed infant (HEI) at six weeks, at 9 months and at the end of all breastfeeding (between 18-24 months). In a recent meta-analysis of loss to follow-up (LTFU) across the PMTCT cascade, about 50% of HIV+ pregnant women are already LTFU by delivery; within 3 months of delivery 33.9% of mother-infant pairs are also LTFU.[3] Consequently, half of pediatric infections are currently estimated to occur in the postpartum period during breastfeeding and fewer than 40% of HEI are tested for HIV at 2-3 months.[4,5] Thus, to achieve an AIDS free generation, effective strategies to improve outcomes of ART in maternal and child health (MCH) clinics are imperative to reduce LFTU among HIV-infected women and their infants and fully maximize adherence to ART. Determinants of this poor performance occur at multiple levels: healthcare delivery systems, providers, and beneficiaries (HIV-infected mothers). Current efforts to improve retention has mainly focused on patient-levels factors. Little is known about the characteristics of health delivery systems or specific health delivery system strategies that will improve long term outcomes of therapy in women who start lifelong ART in MCH clinics.

Quality Improvement Collaborative is one of the most popular methods for organizing sustained improvement efforts at hospitals and ambulatory practices worldwide.[6-8] In the Breakthrough Series approach (henceforth refer to as continuous quality improvement (CQI)),[9] quality improvement (QI) teams from multiple sites across a region or country are brought together to focus on a common problem. Over one or two years, experts in clinical and performance improvement provide the group with periodic instructions and encourage the teams to share lessons learned and best practices. Starting in 2010, South Africa used QI interventions to inform improvement in the health delivery system to successfully scale-up a highly performing national PMTCT program over a short period of time. The use of CQI is thought to have played a key role in the program's success.[10-14] However, despite its popularity, the effectiveness of CQI as a strategy to improve retention in care and long-term outcomes of HIV care in MCH clinics has never been demonstrated in a randomized trial or a well-designed comparative study and it remains to be shown whether the South African experience can be replicated in settings with fewer ressources.[15]

If the CQI interventions are proven to be effective in improving long-term outcomes of therapy in MCH clinics, it will provide PEPFAR and other critical stakeholders with a scalable strategy to strengthen the quality of HIV continuum of care that can be implemented in combination with sustained efforts to expand coverage. Identification of health system delivery characteristics associated with improved long-term outcomes will help determine where and how the CQI interventions can be effectively scaled up to support PEPFAR goal of an AIDS-free generation.

III. Procedures

A. Research Design

This cluster randomized controlled study will be implemented in two phases. In Phase I, we will collect information on the key characteristics of the healthcare delivery system in the facilities participating in the study. We will also strengthen the current monitoring and evaluation system in MCH clinics to establish a robust system capable of collecting individual patient-level data necessary for the timely production of indicators and monitoring of program outcomes. Phase II

will start with the randomization. At the beginning of this phase, using the baseline data collected in Phase I, we will bring together teams from the health district Bureau (responsible for supervision), and from sites in the intervention group to identified key bottlenecks in the care delivery system. The group will also develop and agree on an action plan to modify the priority bottlenecks and the key indicators to include in the quarterly data for actions reports. As part of the final evaluation of the 5-year CQI intervention in participating clinics and health zones of Kinshasa, we will conduct semi-structured in-depth questionnaires with members of CQI teams in MCH clinics and at the health zone level. These qualitative data will allow to evaluate the intervention's implementation process measures. Specifically, qualitative interviews will allow to: 1) Investigate contextual factors important for the way intervention was understood, implemented, and adopted by participating personnel and administrators of MCH clinics and health zones; 2) Examine factors that impact the application, quality, and sustainability of the intervention; 3) Understand the attitudes towards the CQI intervention at different levels (individual, facility, and health zones) and possibilities of its future use and scale-up in DRC to reduce mother-to-child HIV transmission.

This two-phased approach will provide us time to thoroughly assess the health delivery characteristics for Aim 1. The study will be implemented in Kinshasa, Democratic Republic of Congo (DRC) and in collaboration with the University of Kinshasa's School of Public Health (KSPH).

B. Sample

Sampling strategy: According to the National AIDS Program, there are a total of 295 MCH clinics in Kinshasa currently providing PMTCT services. To inform selection, study staff will obtain information on factors that might affect the quality of care provided in each facility including: the type of management, location (health district), number of deliveries, number and type of personnel, and onsite HIV pediatric care. This information will be used to stratify clinics. Within each stratum, a random sample of facilities will be taken within each of the 35 health districts in Kinshasa. This selection scheme is adopted to ensure, for example, that health care facilities at the center of the city, which might have lower patient volumes and more patients with higher socio-economic status than facilities in peri-urban areas, are included in the final sample to ensure that the sampled clinics are representative of all clinics of similar size across the province. Clinics will be excluded if less than 500 pregnant women (less than 5 HIV-infected pregnant women) registered for antenatal care (ANC) in the clinic in 2015. All women diagnosed with HIV during pregnancy or breastfeeding in the participating MCH clinics and initiated on ART during the enrollment period and their HIV-exposed infants will be eligible for the study.

Sample size and Justification: The traditional rule of thumb for sample size in logistic and Cox regression is ten events per predictor.[71-73] However, more recent simulation studies have revealed that serious problems aren't experienced until the number drops below five events per predictor.[74] Given the close association between logistic, Cox, and proportional odds regression models, these studies should provide a reasonable benchmark for sample size determination for our study. Thus, we adopted a rule of seven events per predictor in determining an appropriate sample size. Assuming that 1 contextual-level factor, 2 clinic-level factors, and seven patient-level factors (one socioeconomic, one cognitive, one psychological, one social, one related to accessibility to clinics, and one related to health status) will be significant at the 0.20 level in bivariate proportional odds models and that we'll need five additional terms due to polynomial trends or predictor-by-time interaction effects, our initial models for backward selection will require 105 events. We anticipate that 20% will be lost to follow-up in the first six weeks and 5% will be lost each year thereafter. Thus, for our loss to follow-up model we only require 378 participants.

However, we expect a cumulative MTCT rate of 5% by 24 months that suggests we will need 2,100 participants for this analysis assuming complete follow-up. Accounting for the expected drop-out, we will need to recruit 2100/(0.8*0.95*0.95) = **2,909 participants**. Assuming an average of 10 HIV diagnoses per year at eligible clinics, we will need to enroll in about 105 MCH clinics (3 per districts) in the first three years of the study.

C. Measurement / Instrumentation

Outcomes and measurement: Key programmatic outcomes that will be considered include: loss-to-follow-up (the proportion of HIV+ pregnant women initiated on ART for whom the whereabouts is unknown), retention in care (proportion of participants who are known to be receiving care), non-adherence to scheduled visits (proportion of participants whose whereabouts is unknown or who are in care but have missed at least one scheduled visit over the evaluation period), virological suppression (undetectable viral load), and MTCT rates (proportion of infants born to participating women who are tested positive for HIV).

Table 1. Outcomes and definitions

Outcomes	Definition
Primary	
loss-to-follow-up	Proportion of HIV+ pregnant women initiated on ART for whom the whereabouts is unknown
Timely infant HIV diagnosis	Proportion of HIV-exposed infant with an appropriate HIV test result
Secondary	
Timely ART initiation	Proportion of HIV-infected participants (mother and infant) initiated on ART within two weeks of diagnosis
Retention in care	Proportion of participants who are known to be receiving HIV care
Non-adherence to scheduled visits	Proportion of participants whose whereabouts is unknown or who are in care but have missed at least one scheduled visit over the evaluation period
Virological suppression	Proportion of participants with undetectable viral load
MTCT rates	Proportion of infants born to participating women who tested positive for HIV
Survival	Proportion of participants known to be alive

In 2010, as part of our technical support to the implementation of PMTCT in Kinshasa, we developed and supported the implementation of a mother-infant register in 105 MCH clinics to monitor PMTCT care provided in these clinics. The registry was modeled after the WHO's Three Interlinked Patient Monitoring Systems for HIV Care/ART, MCH/PMTCT (including malaria prevention during pregnancy), and TB/HIV: Standardized Minimum Data Set and Illustrative Tools. The register is used to track important HIV care events among HIV-infected pregnant women and subsequently their HIV-exposed infants, from the first contact with the ANC clinic through delivery and the effective linkage of the mother-infant pairs to HIV care and treatment (C&T) services. The following key information is documented in the register: a maternity code that is used to link mother and infant, address and telephone number, gestational age at HIV diagnosis, date of birth, date of reference to HIV C&T if any, date of first visit at C&T and a code number assigned to the mother at C&T, and other information necessary to calculate PEPFAR's PMTCT indicators. For mother-infant pairs who still need to integrate HIV C&T services after delivery, information on infant feeding practices, cotrimoxazole prophylaxis at subsequent visits, date of first sample collection for early infant diagnosis at six weeks and the result, a second sample collection and result at nine months, and eventually a serological test at 18 months for all infants with HIV-negative PCR results is also documented. For real time use of information in the register, nurses who supervised the implementation of PMTCT technical assistance were each equipped with a laptop including the electronic version of the register (in the open-source software Epi-info) and at each clinic visit, they extracted information for the register into the electronic database and returned the updated database to the central team. The same scheme was used for monitoring in our study on conditional cash transfers with a group of nurses who successfully visited on a regular basis the 90 MCH clinics that were enrolled to extract the data in the electronic database. Because of its success, the register has been adapted by the PNLS for the monitoring of Option B+. We will rely on the register to obtain information on the outcomes with study nurses visiting the clinics on regular basis to extract key information for the study into the database.

For key laboratory tests, CD4 count is generally available free of charge at decentralized locations (over 70 MCH clinics) in Kinshasa and is done at HIV diagnosis and every six months. Viral load measurement is accessible at the national reference laboratory in downtown Kinshasa at a subsidized cost of $25 or at private facilities (Dream, Doctors Without Borders—MSF) at higher cost per test and is recommended for every patient on ART at least once a year. We have budgeted this to ensure that each participant has at least one viral load measurement at enrollment and every year thereafter during this study.

Healthcare system delivery characteristics and measurements: The Facility Audit of Service Quality (FASQ) will be adapted to assess the key organization characteristics of HIV care (including lifelong ART) delivery in participating MCH clinics. FASQ is a relatively low cost approach developed, by MEASURE Evaluation, for district level monitoring or service availability and quality.[68] It provides information on the type of services; status and functionality of infrastructure, equipment and quality of care. The key areas covered include: 1) the range of services offered (HIV testing and counseling, lifelong ART, laboratory), staffing and staff qualifications, operating hours, community linkages, selected administrative and quality control procedures; 2) Facility infrastructure (privacy/capacity, laboratory, delivery, well-child clinics); 3) Readiness to provide quality care in six areas: family planning; STI management; antenatal care; maternal/delivery care and post abortion care; child health/welfare; and HIV prevention, treatment, and care; and the digital maps of facilities and services available. This survey of health facilities participating in the study will be repeated every year thereafter (to monitor change). In each facility, individual-level patient characteristics including: socio-demographic and economic characteristics, beliefs about the health services (cost, quality), cognitive factors (knowledge about HIV and ART, perceived susceptibility and perceived benefit of early ART, perceived self-efficacy for adherence, perceived need for ART and other HIV services), psychological factors (e.g. depression, fear of stigma), social factors (social support – friends, family, male partner involvement in MCH care, intimate partner violence), accessibility to the clinics (distance, transportation, waiting time), and evaluated health status (WHO stage, CD4 count) will also be collected through face to face interviews at enrollment (within one month of ANC registration), after delivery (2-3 days in postpartum ward), at 6 weeks (6 weeks post-partum visit), at 24 weeks (end of exclusive breastfeeding period), and every six months thereafter through the end of all breastfeeding exposure at 24 months. Data on evaluated health status will come from mother-infant pair register. We will use the same research nurses who successfully interviewed and followed 991 mother-infant pairs in our breastfeeding study, at delivery, 1 week, and monthly thereafter and in our just completed conditional cash transfer study.[16,33]

Questionnaires for survey and other interviews are under development and will be submitted for approval once finalized.

D. Detailed study procedures

Intervention – CQI interventions: In MCH clinics randomized to the intervention group, QI initiatives using participatory data-driven approaches and on-site monitoring and supervisory support, will be implemented. At each site, a QI team will be established from among the facility staff (at least one staff each from ANC service, delivery/maternity service, and well-child service). Health district level QI teams will also be set up to ensure oversight of the health facilities' QI initiatives. After randomization, QI teams will be brought together and provided with the baseline data to help them identify

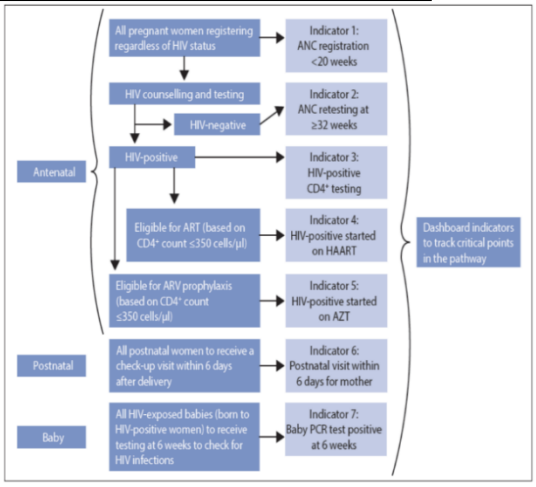

Fig. 6 Prevention of mother-to-child transmission cascade with associated indicators (ANC = antenatal care; ARV = antiretroviral; HAART = highly active antiretroviral therapy; AZT = zidovudine; PCR = polymerase chain reaction). Bhardwaj et al. S Afr Med J. 2014 Mar;104(3 Suppl 1):239-43.

gaps in the service delivery. The team will develop a priority action plan to address the main gaps and agree on a set of key indicators representing critical points in the PMTCT cascade that will be used to monitor the changes resulting from the implementation of the action plan. Thereafter, the health district QI team and a study team member will visit each clinic at least once a month to supervise and support the implementation of the action plan. Every quarter, using data from the monitoring system (Aim 1), the study team working with the provincial coordination of the National AIDS Program (cPNLS) will generate a quarterly report including a color-coded dashboard for tracking changes using the 'traffic light' approach. An indicator will score green when the target has been achieved, yellow/amber when there is a progress from the baseline value without reaching the target, and red when there is no progress or downward movement. Figure 6 outlines the cascade that was followed in South Africa and highlights the indicators used at critical points in the cascade to support tracking progress and identification of gaps in service delivery.[14] A similar cascade will be created with indicators agree upon with the QI teams. The report will be generated for each participating clinics in the intervention group and shared with the cPNLS, the QI teams, and the management of the clinic. QI teams will be brought together to review these indicators, share experience, identify remaining gaps in the service delivery, and develop a new priority action plan for the next quarter.

Statistical Analysis –Aim 1: The primary outcomes for this aim are loss to follow-up and MTCT over the first 24 months of follow-up. Since the characteristics of interest in this aim may vary with time and a substantial proportion of participants may drop out prior to study conclusion or MTCT, both outcomes will be modeled using a proportional odds model for discrete time survival data.[69] At each follow-up time, the proportional odds model assumes that the log-odds that an event (loss to follow-up or MTCT) has occurred by that time point is a linear function of a time-dependent intercept plus covariates, some of which are time-varying. The model also assumes that the odds ratio comparing two different levels of a covariate is constant over time (i.e., proportional odds).

We will use a backward selection methodology to build a proportional odds model for each outcome consisting of contextual, clinic-level, and patient-level predictors. Within clinic-level clustering will be accounted for using Generalized Estimating Equations (GEE). Given the large volume of predictors being considered in this aim, we will only include predictors in our initial models for backward selection if significant at the 0.2 level in a bivariate (single predictor) model. At each step of backward selection, variables insignificant at the 0.1 significance level will be removed from the model.

Statistical analyses – Aim 2: The frequencies of outcomes will be compared between the intervention and control groups using adjusted Pearson's Chi-square.[77] All analyses will be intent-to-treat, meaning that women will be kept in their randomized group independent of whether they actually received (or did not receive) all their care in the group. The intervention and control groups will be compared for baseline prognostic factors and any imbalances that persist after randomization will be adjusted for using logistic regression. Within district- and clinic-level clustering will be accounted for using GEE.

Human subjects' involvement and characteristics

This study will involve HIV-infected pregnant women and their HIV-exposed infants who receive care in one of the maternal and child health clinics providing HIV care in Kinshasa. Clinical record of those participants (mother-infant register) will be accessed by the study team to extract data for the outcomes. In addition those mother will be interviewed on regular basis on sensitive subject

related to their HIV status, social support including relationship with partner. In addition to the discomfort associate with the discussion of such personal topic, there is a potential risk for confidentiality breach associated with the study.

To minimize those risk, all study staff will be retrained on ethical conduct of human subject research. As part of PEPFAR funded routine services for gender-based violence, resource are available at the level of those MCH clinic to provide psychological support for participant who might need them.

In addition to Mother-infant pair, selected health staff of participating clinic will also be interviewed to collect information clinic characteristics. No personal data will be collected from those interview and any potential risk associated with completing the interview is minimal for the participants.

Potential risks

The only potential risk is the potential for confidentially breach as a third person or group of person (study staff) will be informed of the HIV status of participants. However, they will be appropriately trained and regularly supervised to limit this possibility.

To protect from potential breach of confidentiality, all electronic data will be stored on encrypted Iron Drives using only a code to link them to identification information in the register. The link data will be transferred to a secured server (existing) at Albert Einstein College of Medicine using secured FTP channel.

Data management Plan

Data from our study will be stored on a secured server at Albert Einstein College of Medicine. Blood specimen and placental biopsies will be stored in refrigerators (-20^{o}C or – 80^{o}C) at the Kinshasa School of Public Health and be available for studies by other investigators with relevant research questions and appropriate approvals (from the KSPH and the OSU IRBs).

The proposed research will include data from approximately 3000 HIV-infected mothers and their HIV exposed infants. The final dataset will include self-reported demographic and behavioral data from interviews with the subjects, clinical and laboratory data from mother-infant pair registry, blood specimens from the mother and infant and placental biopsies. A specimen collection sheet is added in the annex below. We will be collecting identifying information, including birth date, place and date of delivery. Even though the final dataset will be stripped of identifiers, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, when sharing, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed and results publish.

Informed consent

All subjects will provide written informed consent**.** Parental permission will be obtained for their infant participation.

Benefits of study

The study tests an intervention to improve uptake and adherence to the continuum of HIV services in MCH clinics and long-term outcome of therapy among women who start lifelong ART during pregnancy and breastfeeding. If the intervention is proven to be effective, it can help optimize the effectiveness of ART programs for pregnant women and their HIV-exposed/HIV-infected infants in DRC and elsewhere.

Appendix.

Specimen collection sheet

Timing	Pregnancy and Delivery		Post partum Period	
Study Visit	**Enrollment**	**Delivery**	**6 weeks**	**6, 12, 18, 24 months**
Mother's specimen	Blood	Blood	Blood	Blood
	Urine	Urine	Urine	Urine
Infant's specimen		Cord blood	Blood	Blood
		Placenta biopsie		