Enhanced Virologic Monitoring for Pregnant and Postpartum Women With HIV

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Brief Summary:
The goal of this study is to learn about supporting pregnant and postpartum women living with HIV with treatment adherence. The investigators will conduct a pilot study of an intervention that includes peer counseling about viral load levels and rapid delivery of viral load results. The investigators will evaluate the feasibility of the intervention, and will assess whether it improves viral suppression 6 months following the intervention, compared to historical controls.

Detailed Description:
The investigators will examine the use of more frequent virologic monitoring with enhanced communication around low-level viremia as a strategy to identify and support pregnant and postpartum women at risk of virologic failure. Virologic monitoring itself can reinforce adherence in stable patients, and more frequent monitoring can detect potential adherence challenges early. Notably, low-level viremia is a strong predictor of subsequent virologic failure, and the lowest level associated with perinatal transmission is not known.

The pilot study will run for 6 months at 4 Ministry of Health facilities in Kisumu County, Kenya; 275 participants will be enrolled. Prior to the pilot study, 125 controls will be enrolled prospectively, and 150 controls will be abstracted from records from the prior year.

1. INTRODUCTION/BACKGROUND

Emerging estimates of virologic suppression fall far short of the UNAIDS target among pregnant and postpartum women living with HIV on antiretroviral therapy (ART) in sub-Saharan Africa.[1-6] The UNAIDS 90-90-90 targets to help end the AIDS epidemic are: 90% of persons living with HIV know their status; 90% of those who know their status are on ART; 90% of those on ART are virologically suppressed.[7] Lack of virologic suppression magnifies the risk of disease progression and sexual and perinatal transmission of the virus. The emerging estimates of viremia build on the concerning recent meta-analysis reporting 24% of pregnant women and 43% of postpartum women had suboptimal ART adherence across 51 studies, including 6 from Kenya and 5 each from South Africa and Zambia.[8] Several studies have shown

that the vast majority of viremia experienced perinatally and otherwise is due to suboptimal adherence to ART rather than acquired resistance.[5,9-11] Reaching the third 90 target requires a lifelong commitment to optimal ART adherence. However, pregnancy and the postpartum period introduce significant transitions in daily routines which present both unique challenges to medication adherence and unique opportunities for intervention.

Evidence-based strategies to improve adherence and reduce viremia risk are not always optimally delivered to pregnant and postpartum women most in need of support. For persons with or "at risk" of virologic failure, Kenyan guidelines are in place for enhanced virologic monitoring, enhanced adherence assessment and counseling, and enhanced referrals for nutrition and psychosocial support.[12] However, strategies are needed to identify persons "at risk" of virologic failure, prior to detection of viremia or at the earliest possible time-point of non-suppression, to optimize delivery of timely enhanced support. Such services provided after virologic failure occurs may come too late to prevent the development of resistance or transmission of the virus.

Virologic monitoring can reinforce adherence in stable patients. With frequent monitoring, adherence challenges can be detected and addressed early. In addition, low-level viremia is a strong predictor of subsequent failure, and the level associated with perinatal transmission is not known. Thus, using a sensitive viral load assay (lower limit of detection ≤100 copies/mL) every 3 months in pregnancy and up to 6 months postpartum could provide an opportunity to provide enhanced support early.

The scientific premise of this proposal is that enhanced virologic monitoring has the potential to improve health outcomes in the highest risk patients. Early adherence support for pregnant and postpartum women most at risk of viremia could have an important impact on reaching the UNAIDS third 90 target in this population, and ultimately on improved maternal and infant outcomes among women living with HIV.

2. OBJECTIVES

Objective: Evaluate the implementation and potential impact of risk assessment with enhanced virologic monitoring to facilitate targeted, evidence-based adherence support to pregnant/postpartum women at risk of viremia in a pilot study in western Kenya.

3. DESIGN AND METHODOLOGY

The study will be conducted within MoH clinics, in Kisumu County, Kenya. Kisumu County is one of the regions of Kenya most affected by the HIV epidemic: in 2015, adult HIV prevalence (age 15-49) was 20% and the rate of perinatal transmission was 20%.[48]

In a 6-month pilot study, we will evaluate the implementation and potential impact of enhanced virologic monitoring for pregnant and postpartum women living with HIV to reduce the risk of viremia and loss from care. Prior to the pilot study, we will sample 2 control groups: 1) 125 women will be prospectively enrolled at the pilot study sites (as part of the CAPS mobility sub-study), and 2) 150-320 women will be randomly selected from de-identified electronic medical records.

(a) Study sites: 2-4 clinics will be selected for the pilot study.

(b) Study populations: All women seeking care at these sites who are on ART ***and***, either in their 3rd trimester of pregnancy, in the maternity ward for delivery, or within the first 6 months postpartum are eligible. Our rationale for this time range is: (1) Late pregnancy and delivery are critical periods for prevention of mother to child transmission. (2) 0-6 months postpartum is a period highly susceptible to disengagement from care among women living with HIV.

(c) Sampling: For prospectively enrolled controls and pilot study participants, to ensure adequate representation from each facility and to avoid seasonal differences by site, we will conduct recruitment at each site simultaneously, visiting each site within any given week in which recruitment is done, to the best our ability. We will invite all women attending clinic on days of recruitment at each site, and will trace all women late for visits that were due on those recruitment days. Controls selected from records only will be randomly sampled from eligible women with viral loads scheduled for collection in the 6 months prior to the pilot study.

Recruitment.
Building on our established relationships with MoH and clinic leadership in Kisumu, we will work collaboratively with these teams to ensure on-site research staff support with patient recruitment, including access to patients, clinic records, and registers. We will attempt to recruit, consent, enroll, and conduct baseline visits in conjunction with a clinic visit to reduce the burden on participants. For participants that prefer to meet elsewhere, we will arrange a separate time and place to meet at their convenience. For those who are late for visits, mentor mothers will use all available phone numbers and location data in the clinical record to locate the individual. For participants who are hard to reach, we will train mentor mothers with established tracking methods to determine potential relocation information about the participant.[51]

(d) Procedures:
Study visit
For prospectively enrolled controls and pilot study participants, following participant consent, study staff/providers will collect sociodemographic, clinical, and mobility questionnaires from patients directly and from records, and a blood sample to test viral load. Study staff/providers will have access to clinical records during the study visit and can query patients and clinical staff regarding key clinical variables if data are missing from records. Sociodemographic data and mobility measures will be collected directly from the participant. Data will be collected directly into REDCap, a secure platform for building and managing datasets which has an off-line data collection option enabling use in settings where internet access may be limited.

For participants who are reached and consented outside of the clinic via tracing, data will be collected in a location convenient to the patient.

Samples collected for viral load testing will immediately be stored in a cooler bag and will be tested for HIV RNA levels with Cephied's GeneXpert® technology, Xpert HIV-1 Viral Load on the same day.

Intervention
Our enhanced virologic monitoring intervention includes 3 components: 1) More frequent viral load collection than standard of care, 2) Rapid return of viral load results, 3) Enhanced viral load counselling, including about low-level viremia. These are detailed below.

1) More frequent viral load collection
Our research assistants will be trained in phlebotomy. All participants who have not had a viral load collected within the prior 80 days will have a blood sample collected at baseline for viral load testing. Those who enroll in the first 3 months of the pilot study period will be eligible for a follow-up visit within the 6-month pilot study period, and will have viral load assessed again at the 3-month follow up visit.

2) Rapid return of viral load results:
Mentor mothers will be trained to return viral load results to patients with scripted messaging according to viral load level (undetectable, low-level viremia (50-1000), high viral load (>1000)). Patients will be offered a choice of the mode of delivery, including text, phone, or in-person. Detectable viral loads will not be delivered by text, and women with high viral loads may be asked to return to the clinic for in-person counselling.

3) Enhanced viral load counselling
Mentor mothers will reinforce adherence with all patients with undetectable levels via scripted messaging to reward and encourage healthy behavior. For those with any detectable levels, mentor mothers will be trained to provide targeted counseling about low-level and higher viral loads. Women who report significant psychosocial barriers will be referred to a social worker.

Study Measures.

Baseline characteristics.
To assess objective 3 and the objectives of the sub-study, we will collect information about women's baseline characteristics (individual and social) that we believe may be confounders of the associations we plan to estimate (ie., the impact of enhanced virologic monitoring on subsequent viremia; the impact of mobility on viremia and retention in care). These baseline characteristics will include the following, and the surveys are included as an appendix to this protocol:

- Sociodemographic and health information (e.g., marital status, education, mobility)
- Clinical records data abstraction (pregnancy history, HIV history – from records)
- Household food insecurity scale (HFIAS)
- Perceived stress scale (to measure psychosocial stress)
- Edinburgh depression scale (to measure perinatal depression)

If, during the depression questionnaire, a study participant expresses an intent to harm themselves or scores 11 or higher,[52] they will be referred to social services (e.g., social worker, psychiatrist, other mental health provider) for further assessment on the same day. Because this questionnaire will be collected on REDCap, the score will be automatically generated once the form is completed. The social service staff member is not part of the study team. The study will cover the cost of an initial consultation for patients who would benefit from further assessment up to ~2000 KShs or ~$20 USD. If further care is recommended, the participant will be responsible for those costs. We note these potential costs in the informed consent form.

HIV care outcomes.
The viral loads collected as part of the intervention will guide the counselling that is provided during the study. Study outcome viral loads will be routine care viral loads that are collected (1) within the 6 months following the control participants enrollment (and only) study visit, for prospectively enrolled controls, (2) within the 6 months prior to the pilot study for controls

retrieved from electronic records, and (3) within the 6 months following the pilot participants last study visit. The study team will work together with the clinical teams to ensure these viral load outcomes are measured and recorded according to national guidelines. Viremia will be defined as any detectable levels of HIV RNA. Suboptimal care engagement will be defined as late for a clinic visit by 30 days or more.

Implementation outcomes.
Enola Proctor has proposed a taxonomy of implementation outcomes to inform systematic and scientifically rigorous measurement of implementation success.[53] The pilot study outcomes summarized in Table 1 are outcomes which Proctor has identified as most salient to the early stages of implementation, while gaining training in the measurement of later stage outcomes to incorporate in my future research.

Table 1. Implementation outcomes and method of measurement in the pilot study

Outcome	Method of measurement	When measured
Acceptability (provider satisfaction, facilitators, barriers)	• Survey	End of pilot
Adoption (uptake, intention)	• Record for each enrolled participant 1. whether the viral load monitoring was conducted on schedule 2. what action was taken in response to low-level viremia 3. reasons for no action	Daily throughout follow-up
Appropriateness (perceived fit)	• Survey	End of pilot
Feasibility (practicability, utility)	• Survey	End of pilot

The PIs and research team will lead training sessions for mentor mothers and research assistants prior to the start of the study, followed by periodic (at least monthly) follow-up sessions to reinforce initial plans and revise strategies as needed. These data will be entered into de-identified REDCap databases containing only anonymous study IDs. A separate secure list linking study IDs to clinic IDs will be maintained in order to later link these records to virologic outcomes. At the conclusion of the study, surveys will be administered to key stakeholders and care providers at the sites (n=~10) to measure acceptability and feasibility, and semi-structured in-depth interviews will be conducted to further assess acceptability, appropriateness and intentions. Interview guides will be informed by a rapid analysis of survey data and assessments of adoption.

Evaluating the potential impact on maternal viremia. We acknowledge that this pre-post analysis will not reflect a causal effect of the pilot on viremia risk, as any observed differences could be due to temporal or other factors. This pilot study, rather, aims to explore the *potential* impact while gathering critical data on the feasibility and acceptability of the intervention to inform future research.

4. DATA MANAGEMENT

Analyses of implementation outcomes. Analyses will summarize acceptability and feasibility survey results, summaries of adoption, as well as the clinical and sociodemographic characteristics of the women seen at the clinic during the pilot study, using descriptive statistics.

Evaluating the potential impact on maternal viremia. The frequency of viremia in the year preceding the pilot to the frequency among women seeking care during the pilot will be

compared with logistic regression, adjusted for baseline differences in clinical and demographic characteristics.

5. ETHICAL CONSIDERATIONS

Study databases will only include anonymous study IDs. In order to link baseline patient characteristics to viral load outcomes, we will maintain a separate secure list linking study IDs to clinic IDs. Only the PI and research team will have access to this linked ID list, and will use it to ensure data quality.

Potential risks will be minimal, and could include 1) discomfort having additional blood draws for additional viral load testing, and 2) loss of privacy or social harms due to loss of privacy.

Informed consent: We will obtain written informed consent from all women participating. Clinical care remains at the discretion of the treating clinician. The informed consent forms will describe the purpose of the study, the types of activities that will be conducted, and the risks and benefits of participation.

Protections Against Risk: Every effort will be made to ensure the privacy of participants. All study paper and study databases will only include de-identified data and study IDs. Lists matching study IDs to clinic IDs and provider names will be maintained in a separate REDCap project only accessible to the PI and the research assistant. Recording devices and paper informed consent forms, interview and observation notes, and any other paper materials containing human subject data will be stored in a locked file cabinet in a locked room. Audio recordings and interview transcripts will be stored in secure, password-protected, MyResearch online storage space to allow access in Kenya and San Francisco. MyResearch is supported in a secure, professional data center, locked and guarded 24x7 with UCSF badge access required for physical entry. Data exists on a private network with its own firewall. REDCap is housed in a locked and guarded data center. Entrance to the data center requires triple factor authentication: use of a card key to unlock the data center door, biometric authentication and a second card key lock secures the cage that the servers reside within. The security of the data center is monitored by a security camera system. REDCap servers are guarded by multiple firewall and intrusion detection systems. All electronic connections to the REDCap environment are encrypted.

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