Reducing time to spaced-out appointments for newly-diagnosed people living with HIV: a pilot study

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STUDY TITLE
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A. OVERVIEW OF THE STUDY

Reducing time to spaced-out appointments for newly-diagnosed people living with HIV: a pilot study is the third part of a three-part research grant entitled, ***Minimizing losses from HIV care under Treat All in Rwanda***. This research grant is funded by the US National Institute of Health's (NIH) National Institute of Mental Health (NIMH) and was awarded to the Albert Einstein College of Medicine, NY, US, working in close partnership with Rwanda Military Hospital (RMH). This grant is nested within the ***Central Africa International Epidemiology Databases to Evaluate AIDS (CA-IeDEA)***, a research consortium led by Albert Einstein College of Medicine and RMH. The research proposed in this protocol will leverage the existing data and resources of CA-IeDEA, the strong and successful partnership between Albert Einstein College of Medicine and RMH, and ongoing support from an advisory committee that includes senior members of the Rwanda Biomedical Center (RBC). The protocol for CA-IeDEA has previously been approved by the Rwanda National Ethics Committee (RNEC) and the IRB of the Albert Einstein College of Medicine.

Most countries in sub-Saharan Africa have adopted differentiated care models for people living with HIV (PLWH), including Rwanda. Current Rwandan HIV guidelines classify newly-diagnosed PLWH as "unstable", requiring frequent visits to the health facility. Before they can advance to being "stable" patients, with spaced-out appointments that allow them to visit the health facility less often, they must be on antiretroviral therapy (ART) for 18 months and virally suppressed on two consecutive measurements. Patients face multiple barriers to attending frequent appointments including structural issues (such as distance to the health facility, transportation cost, long waiting times) and facing stigma while traveling to and while at the health facility. Reducing the time newly-diagnosed PLWH spend in the "unstable" category could potentially decrease the burden on patients and the health facility and potentially decrease the costs of frequent appointments. We therefore propose a pilot study to examine the effect of reducing the time from diagnosis to advancement to the "stable" category from 18 to 6 months. We will randomize participants to one of three arms: 1) early spaced-out appointments after 2 suppressed viral loads (advancement to the "stable" category at 6 months if 2 consecutive viral loads are suppressed); 2) early spaced-out appointments after 1 suppressed viral load (advancement to the "stable" category at 6 months if a single viral load is suppressed) or usual care (advancement to the "stable" category at 18 months). We will compare study arms with respect to viral suppression at 12 months (primary outcome) and appointment/pharmacy adherence (secondary outcome). We hypothesize that reducing the time to the "stable" category with spaced out appointments will be feasible, acceptable, not inferior to 18 months with respect to viral suppression or adherence, and will be cost-effective.

B. OVERVIEW AND SPECIFIC AIMS

The overarching goal of this research is to increase retention on antiretroviral therapy (ART) among people living with HIV (PLWH) in sub-Saharan Africa, the region most affected by the global HIV pandemic.[1] With the goal of ending the pandemic, the UNAIDS "90-90-90" targets for 2020 are that 90% of all PLWH know their HIV status, 90% of people with diagnosed HIV infection receive sustained ART, and 90% of all people receiving ART achieve viral suppression.[2] While Rwanda is very close to achieving these targets[3], certain groups such as men and younger PLWH are at higher risk of poorer outcomes. Reducing barriers to initiating and adhering to therapy is thus paramount to ensuring all PLWH in Rwanda succeed in HIV therapy.

In the qualitative work that we have conducted as part of the current research grant, patients reported multiple barriers to attending appointments including structural issues (transportation cost, distance to the health center, long waiting times) and facing stigma while traveling to and while at the

health center.[4] Reducing the frequency of medical appointments for patients who are clinically stable in care could potentially reduce the burden faced by these patients. Indeed, the WHO recommends such an approach to address the specific needs of different groups of PLWH and reduce burden on the health system.[5] While WHO guidelines define "clinically stable" patients as those on ART for 1 year with 2 consecutive viral loads,[5] research studies as well as HIV programs in sub-Saharan Africa have defined "clinically stable" PLWH as those on ART for shorter intervals (i.e. 6 months after diagnosis) and/or with only 1 suppressed viral load.[6-8] *However, to date, no studies to our knowledge have compared how a shorter time on ART or only 1 viral load measurement compare to the current WHO guidelines*.

The objectives of this study are to thus pilot test the effect of reducing time to spaced-out appointments from 18 to 6 months for newly-diagnosed PLWH in Rwanda. This is a critical time to conduct this work, as most African countries have adopted differentiated care models. Rwanda, where this study is based, was among the first countries to implement Treat All as a national policy and remains a leader in HIV outcomes. To better understand the effects of early spaced-out appointments as well as the degree of viral load monitoring needed to determine stability, we will conduct a 3-arm pilot intervention study. We will enroll 90 patients: 30 will be randomized to 6-month advancement to spaced out appointments after 1 suppressed viral load (at 5 months after enrollment) ("*Early 1*"); 30 will be randomized to 6-month advancement to spaced-out appointments after 2 suppressed viral loads (at 3- and 5-months after enrollment) ("*Early 2*"); and 30 will be randomized to continue in usual care ("*Usual care*"). We will compare the study arms with respect to viral suppression at 12 months after enrollment (primary outcome) and appointment/ pharmacy adherence (secondary outcome). We hypothesize that reducing the time to the "clinically stable" phase to 6 months will be feasible, acceptable, not inferior to usual care with respect to viral suppression or adherence, and will be cost-effective. The specific aims of this study are:

Aim 1: measure the preliminary efficacy, feasibility and acceptability of early spaced-out appointments.

a. Preliminary efficacy: We will compare intervention arms to the usual care arm with respect to 12-month viral suppression (primary outcome) and appointment/pharmacy adherence (secondary outcomes). *Hypothesis: We hypothesize that outcomes will not be inferior in the intervention arms compared to the usual care arm.*

b. Feasibility. We will examine process measures (patient enrollment, patient waiting time, staff effort) at the end of the trial.

c. Acceptability. We will assess patient and care provider satisfaction at the end of the trial.

Aim 2: measure the cost-effectiveness of early spaced-out appointments. We will collect patient- and health center data on costs, including transportation, specimen testing, and potential cost of downstream outcomes. *Hypothesis: we hypothesize that short-term cost will be higher in the "Early 2" arm compared to "Early 1" and "Usual care," but that long-term costs will be lower in the "Early 1" and "Early 2" arms compared to the "Usual care" arm.*

C. RESEARCH DESIGN AND METHODS

Overview

We will recruit approximately 90 patients and randomize them to one of three arms (early spaced-out appointments after 1 suppressed viral load – *Early 1*; early spaced-out appointments after 2 suppressed viral loads – *Early 2*; *care as usual*). We will follow patients for 12 months after enrollment. We will compare arms with respect to viral suppression, appointment adherence, and overall cost, as well as collect data on feasibility and acceptability. These findings will inform future Rwandan policy regarding differentiated care for people living with HIV and provide important evidence for global HIV control efforts.

Central Africa-IeDEA

The NIH-funded Central Africa International Epidemiology Databases to Evaluate AIDS (CA-IeDEA) consortium is the largest observational HIV research network in Central Africa. In Rwanda, 10 public health centers (HC), one referral hospital and one private HIV clinic collaborate with CA-IeDEA, under the oversight of Rwanda Military Hospital (RMH), a referral and research hospital in Kigali. Three of these health centers (Gikondo, Kicukiro, Kanombe/RMH) will participate in this pilot study.

Study setting

The proposed study will be carried out in Gikondo HC, Kicukiro HC, and Kanombe/RMH, as well as Remera HC (a site that does not participate in IeDEA). These health facilities are located in Rwanda's capital, Kigali, and provide care to approximately 6,000 PLWH. In total, approximately 300 newly-diagnosed patients enroll in these three health facilities each year.

Study participants, recruitment and enrollment

- **Inclusion/exclusion criteria**: *Inclusion* criteria for the study are: 1) ≥15 years; 2) newly-diagnosed with HIV; 3) enrolled in care at study health facility; 4) initiated ART. *Exclusion criteria* are: 1) planning on moving away from health center/Kigali in the next 12 months; 2) unable to provide informed consent; 3) enrolled in care while pregnant; 4) co-infected with tuberculosis; 5) concurrent known mental health or substance use disorder.
- **Recruitment**: A study research assistant will work with staff at the health facility to identify persons who are newly-diagnosed with HIV and may be eligible for the study. We will have clinic nurses inform potentially eligible patients about the study during appointments and provide study contact information. We will also put up posters in health facilities with study information.
- **Screening procedures:** The research assistant will meet with interested participants to describe the study and offer enrollment during a follow-up appointment after their enrollment into care. Patients who are interested in participating in the study, who meet criteria and who provide written informed consent will be enrolled in the study and be randomized to either the intervention arms or the standard of care arm.
- **Randomization:** randomization will be stratified by age (<24 vs ≥24) and by clinic and occur in blocks of 4-8, with 1:1:1 allocation of the three study arms.

Clinical visits: Intervention and usual care arms

- **Early spaced-out appointments after 1 suppressed viral load – *Early 1.*** Patients enrolled in this arm will pick up medications monthly at the pharmacy and attend clinical appointments every 3 months until 6 months after entering HIV care. They will have a viral load measured at month #5 after entering HIV care. If their viral load is suppressed, they will advance to spaced out appointments at month #6 after entering HIV care, picking up medications every 3 months and attending clinical appointments every 6 months.
- **Early spaced-out appointments after 2 suppressed viral loads – *Early 2*.** Patients enrolled in this arm will pick up medications monthly at the pharmacy and attend clinical appointments every 3 months until 6 months after entering HIV care. They will have a viral load measured at month #3 and #5 after entering HIV care. If both viral loads are suppressed, they will advance to spaced out appointments at month #6 after entering HIV care, picking up medications every 3 months and attending clinical appointments every 6 months.
- **Standard of care – *Usual care*.** Patients enrolled in this arm will pick up medications monthly at the pharmacy and attending clinical appointments every 3 months for the duration of the study. They will have a viral load measured at month #5 after entering HIV care.

Research visits

- All participants will have research visits at baseline (study enrollment, which will occur in the first month after enrollment), month #6 after enrolling in HIV care, and month #12 after enrollment. Participants will undergo interviews at all study visits, and will undergo follow-up viral load testing

at 12 months. Participants will be compensated 8,000 Rwandan francs (RWF), approximately $8 USD, at each visit.

Table 1. Study and research visits													
	Assessment period (month)												
Study arm	0	1	2	3	4	5	6	7	8	9	10	11	12
Early 1													
Clinic visits	x			x			x						x
Pharmacy pick-up	x	x	x	x	x	x	x			x			x
Viral load						x							x
Early 2													
Clinic visits	x			x			x						x
Pharmacy pick-up	x	x	x	x	x	x	x			x			x
Viral load				x		x							x
Usual care													
Clinic visits	x			x			x			x			x
Pharmacy pick-up	x	x	x	x	x	x	x	x	x	x	x	x	x
Viral load						x							x
Research visits													
All arms		x					x						x

Data sources and collection:

- **Questionnaires/Surveys**: questionnaires will be administered to participants at each research visit (enrollment, 6 months, 12 months) using RedCap technology. We will collect data on demographics, HIV risk and diagnosis, medication adherence, quality of life, patient satisfaction, and anticipated or experienced HIV-related stigma.
- **Medical records**: we will extract data from participants' medical records, including HIV diagnosis date, ART initiation date, appointment and pharmacy visit dates, and medication regimen.
- **Laboratory/blood testing**: all participants will undergo lab testing including creatinine, CD4 count, liver function testing at study enrollment. Participants will undergo viral load testing at intervals noted above and at the study conclusion at 12 months. Tests will be processed at Rwanda Military Hospital's lab and results will be inputted into study databases and clinical registers.

Table 2. Data collection				
Measure	Instrument/source	Research visit		
		Baseline	6 mo	12 mo
REDCAP Questionnaire				
Socio-demographic information	Sociodemographic form	x		
Quality of life	EQ-5D[9]	x	x	x
Patient satisfaction with care	Patient satisfaction with care[10]	x	x	x
Other healthcare utilization	Other healthcare utilization form	x	x	x
Medication adherence	7-day medication adherence recall		x	x
HIV stigma - anticipated	Earnshaw & Chadoir[11,12]	x	x	x
HIV stigma - experienced	HASI-P[11,13]	x	x	x
Patient costs/expenditures	Patient expenditure form	x	x	x
Medical record				
Enrollment data (date of diagnosis, date of enrollment, date of ART)		x		
Appointment adherence		x	x	x
Pharmacy visit adherence		x	x	x
ART regimen		x	x	x
Laboratory				
Baseline laboratory test (creatinine, CD4, liver)		x		
Viral load		Per protocol above		

Data management

Data collected during from patient questionnaires during study visits will be entered directly by study staff into the RedCap database using the participant's study ID. Data from the medical records (paper charts) will be regularly extracted and entered into the RedCap study database using the participant's study ID. Laboratory test results will be obtained from the Rwanda Military Hospital lab and will be entered into the RedCap study database using the participant's study ID. Results will also be provided to the participants' health center.

The RedCap database will be housed on an encrypted, password-protected computer at Rwanda Military Hospital. Only project staff will have access to this database. All patient identifiers will be scrubbed from the database and participants will only be referenced by a study ID. A crosslink from study ID to patient identifiers will only be available to study personnel in a separate password-protected folder stored on a different encrypted computer at Rwanda Military Hospital. Participant's consent forms will be stored separately from research data in locked file cabinets on site at Rwanda Military Hospital.

Main outcome variables

- **Preliminary efficacy**: *Primary outcome* is viral suppression (defined as viral load <200) at 12 months (yes/no). *Secondary outcome* is appointment and pharmacy adherence (attended all appointments/missed ≥1 appointment).
- **Feasibility/acceptability**: patient satisfaction with appointment schedule, health worker satisfaction with appointment schedule, patient experiences of stigma
- **Cost**: we will collect data on patient-level costs borne by patient or relatives of the patient towards their care (i.e. transportation to clinic, missed days of work). To ascertain the cost to the health facility, we will estimate fixed (i.e. equipment, human resources) and variable (i.e. type and number of visits, laboratory tests, inpatient care) costs to care.

Data analysis

- **Assessment of randomization:** we will compare all covariates between the 3 study arms, using t-tests (or non-parametric tests) for continuous variables and chi-square (or Fisher tests) for categorical variables.
- **Preliminary efficacy:** We hypothesize that viral suppression and appointment/pharmacy adherence will be similar across the 3 study arms. We will first compare proportions of patients achieving viral suppression and attending all appointment/pharmacy visits using chi-square tests. We will use generalized estimating equations to estimate risk differences, risk ratios and associated 95% confidence interval for the effect of each intervention arm compared to the control. The non-inferiority limit will be set at 10%. Because of the small number of participants we will be able to enroll in this pilot study, it may not be sufficiently powered to detect a statistically significant differences in outcomes. However, the findings and the effect size obtained from this study will provide key results on intervention feasibility and guide a future, larger study to test intervention efficacy.
- **Cost analysis:** We hypothesize that the intervention arms will result in reduced patient-level and health-center costs. Outcomes will include: (a) annual cost per patient in each cohort/arm (per patient year cost); and (b) cost-effectiveness of the intervention arms compared with usual care.

D. PROTECTION OF HUMAN SUBJECTS

Human subject involvement and characteristics

- **Inclusion/exclusion criteria:** *Inclusion* criteria for the study are: 1) ≥15 years; 2) newly-diagnosed with HIV; 3) enrolled in care at study health center; 4) initiated ART. *Exclusion criteria* are: 1) planning on moving away from health center/Kigali in the next 12 months; 2) unable to

provide informed consent; 3) enrolled in care while pregnant; 4) co-infected with tuberculosis; 5) concurrent known mental health or substance use disorder.

- **Rationale for inclusion/exclusion criteria:**
  - We selected our inclusion criteria to best represent adult patients living with HIV receiving care in Rwandan health facilities and who could be eligible for spaced-out appointments.
  - We are including participants aged 15-18 as this population receives HIV care together with PLWH >18 years of age in the same health facilities. PLWH aged 15-24 are at particular risk of poor clinical outcomes, and therefore including participants between ages 15-18 will allow us to obtain preliminary data on whether spaced-out appointments could be beneficial for this group. Participants <18 years of age will be required to provide assent, with a parent or guardian providing consent, in order to participate in the study.
  - We will not recruit pregnant women for this study. Although they could benefit from spaced-out appointments, the health system is structured in such a way that they would need to attend more frequent appointments for antenatal and postnatal care, thus reducing the potential effect of spaced-out appointments. Likewise, we will not enroll patients simultaneously diagnosed with tuberculosis as they are required to attend clinic appointments frequently throughout their treatment course.

Potential risks

- **Confidentiality:** Patients who participate in this study may be concerned that the confidentiality of their health information or their job performance may be compromised. During the informed consent process we will inform patients that all data will be kept confidential and that identifying information (on the informed consent) will be kept separately from interview data. We have outlined our procedures to maintain confidentiality below.
- **Inconvenience and discomfort associated with interviews:** Because participants will be queried about HIV and receipt of health care, it is possible that such questions could produce anxiety or discomfort. During the informed consent process, participants will be told that they may withdraw from the study if they find the questions troubling.
- **Discomfort associated with blood tests:** Participants will provide plasma blood samples on several occasions. Although these are diagnostic tests that are typically performed as part of their routine care, they may still cause some anxiety or discomfort. Participants will be told that they may refuse blood tests if they find them troubling.
- **Fear that refusal to participate will affect care or employment:** In this study, participants' health care is based at the health center where the study is taking place. During the informed consent process, we will clearly explain that participation in the study is voluntary and that participants' health care or employment are not contingent on their participation in the study.
- **Potential for poorer HIV clinical outcomes:** While we hypothesize that viral suppression and appointment adherence in the intervention arms will be non-inferior to usual care, it is possible that less frequent appointments early in the post-diagnosis period will lead to poorer outcomes. All health centers participating in this study have detailed protocols for patients who do not attend appointments, and if a patient fails to attend an appointment these protocols will be activated. Similarly, if a patient is not virally suppressed at any point during the study, typical adherence intensification efforts will be utilized at study centers.

Protection against Risks

- **Recruitment and informed consent**: All recruitment and consent processes will be approved by the Albert Einstein College of Medicine Institutional Review Board and the Rwanda National Ethics Committee prior to starting recruitment. A research assistant or one of the investigators will obtain informed consent in Kinyarwanda prior to enrollment in the study. This will entail a discussion on the study rationale, procedures and potential risks and benefits, as outlined in the

accompanying informed consent document.

- **Breach of confidentiality:** We will take the following steps to protect against breach of confidentiality:
    - Paper study records (i.e. informed consent documents) will be kept in locked file cabinets with access limited to study staff.
    - Electronic study records (i.e. study databases) will not contain any identifying information
    - Study databases will be maintained on encrypted, password-protected computers to which only study staff will have access
    - We will utilize a system that prevents linking of sensitive material to participants' personal identifiers. We will have a "name-based" system and "ID-based" system that will remain separate. In the name-based system, all documents that have patient identifiers (e.g. consent forms) will be filed together. Any files that do not include identifying information or signatures will only use participants' unique IDs (rather than names) and will be filed separately from name-based documents. All forms will contain either participants' names or their unique study IDs, but not both. There will only be one electronic document that links participants' names to their study IDs. Only the study staff will have access to this document which itself will be password protected and kept on a password-protected computer.
    - All research staff will complete the Collaborative Institutional Training Initiative (CITI) computer-based training program, which includes a specific module about privacy and confidentiality and will be trained in standard operating and study-specific protocols regarding protection of confidentiality.
    - Publication or presentation of study results will not identify subjects.

Potential benefits

Participants in the intervention arms may benefit from attending appointments and pharmacy pick-ups less frequently. If effective, our study has implications for improving health outcomes for people living with HIV in sub-Saharan Africa. This could have important individual and public health benefits with improved individual health and lower HIV transmission rates. Participants will receive a stipend (8,000 RWF, or approximately $8 USD) for their participation.

Risk/benefit ratio

Our study has the potential to improve outcomes for people living with HIV in sub-Saharan Africa. Given the steps that we take to minimize the chances of breach of confidentiality and other risks, participating in this study presents low risk and the risk/benefit ratio is favorable.

Data Quality Control

To maintain confidentiality and data integrity, we will take the following steps:

- We will remove patients' protected health information and provider identifiers from all data before conducting analyses.
- Study data will be kept in a password-protected, encrypted file on password-protected servers. No one but the study team will have access to study data.
- Publication or presentation of study results will not include information that would allow for identification of providers or patients.

Data safety monitoring plan

This is a low-risk study and will not have a data safety monitoring board. The PI and co-investigators will continuously monitor recruitment, retention, adverse events, protocol deviations, and protocol violations. All investigators will meet monthly (by videoconference) to discuss recruitment, retention,

data quality and any adverse events, making corrective plans as necessary. No interim analyses are planned for this pilot study.

E. PARTICIPATION OF CHILDREN

We will include participants aged 15-18 years as this population receives HIV care together with PLWH >18 years of age in the same health centers. PLWH aged 15-24 are at particular risk of poor clinical outcomes, and therefore including participants between ages 15-18 will allow us to obtain preliminary data on whether spaced-out appointments could be beneficial for this group. Participants <18 years of age will be required to provide assent, with a parent or guardian providing consent, in order to participate in the study. Participants aged 15-18 years will otherwise continue to receive clinical care in their usual care settings.

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APPENDIX 1. STUDY TIMELINE AND BUDGET

A. Study Timeline

Year	2020			2021				2022	
Quarter	2	3	4	1	2	3	4	1	2
Obtain ethical approval									
Participant recruitment and baseline visits									
Follow-up (6- and 12-months)									
Data analysis									
Manuscript preparation									