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Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for an exploratory, unblinded randomized control study.

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ABSTRACT

Introduction: Current HIV guidelines recommend differentiated service delivery (DSD) models that allow for fewer health center visits for clinically stable people living with HIV (PLWH). Newly-diagnosed PLWH may require more intensive care early in their treatment course, yet frequent appointments can be burdensome to patients and health systems. Determining the optimal parameters for defining clinical stability and transitioning to less frequent appointments could decrease patient burden and health system costs. The objectives of this study are to test the effect of: 1) reducing the time to DSD from 12 to 6 months after antiretroviral therapy (ART) initiation, and 2) reducing the number of suppressed viral loads required to enter DSD from two to one.

Methods and analyses: The present study is an exploratory, unblinded trial taking place in three health facilities in Kigali, Rwanda. Current Rwandan guidelines require PLWH to be on ART for ≥12 months with two consecutive suppressed viral loads in order to transition to less frequent appointments. We will randomize 90 participants to one of three arms: entry into DSD at six months after one suppressed viral load (N=30), entry into DSD at six months after two suppressed viral loads (N=30), or current standard of care (N=30). We will measure feasibility, acceptability and preliminary efficacy of this intervention; clinical outcomes include viral suppression at 12 months (primary outcome) and appointment attendance (secondary outcome).

Ethics and dissemination: This clinical trial was approved by the institutional review board of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee. Findings will be disseminated through conferences and peer-reviewed publications as well as meetings with stakeholders.

Trial registration: Clinicaltrials.gov [NCT04567693]

Strengths and limitations of this study

- A randomized, controlled trial examining clinical outcomes of newly-diagnosed people living with HIV who transition to differentiated service delivery models after shorter intervals in care or fewer viral load measurements will provide important evidence to inform HIV program implementation in Rwanda as well as globally.
- A three-armed study will be able to simultaneously assess the impact of: 1) reducing the time to differentiated service delivery from 12 to 6 months after antiretroviral therapy initiation, and 2) reducing the number of suppressed viral load measurements required to enter differentiated service delivery from two to one.
- Consideration of experienced and anticipated stigma as well as patient expenditures will provide additional information on the impact of this model of care.
- The unblinded nature of this trial may lead to bias in subsequent clinical management and outcome ascertainment.
- The setting of the trial (urban health facilities in the capitol city of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa) may limit the generalizability of our findings.

INTRODUCTION

With the goal of ending the pandemic, the UNAIDS "90-90-90" targets for 2020 are that 90% of all people living with HIV (PLWH) know their HIV status, 90% of people with diagnosed HIV infection receive sustained antiretroviral therapy (ART), and 90% of all people receiving ART achieve viral suppression. [1] To this end, in 2015 the World Health Organization (WHO) recommended in its Treat All guidelines that all PLWH initiate ART as quickly as possible after diagnosis.[2] Since implementation of its Treat All policy in 2016, Rwanda has nearly achieved UNAIDS 90-90-90 targets,[3] yet groups including men and younger PLWH remain 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.

To optimize HIV program outcomes under Treat All, Rwanda simultaneously introduced differentiated service delivery (DSD) models to align services with the variable needs and preferences of different groups of PLWH.[4] A key element of this strategy is the classification of PLWH into "stable" and "unstable" categories. Stable PLWH - adults on first- or second-line ART for ≥12 months with two consecutive suppressed viral loads - can collect ART every 3 months (rather than monthly) and attend clinical appointments every 6 months (rather than quarterly). Individuals in the unstable category include newly diagnosed PLWH (<12 months on ART), women who are pregnant or lactating, patients with concurrent mental health disorders, and PLWH who are not virally suppressed.

Our earlier research in Rwanda identified frequent appointments as burdensome to newly-diagnosed PLWH because of structural issues such as transportation cost and long wait times, as well as stigma experienced while traveling to and while at the health center.[5] Modifying the definition of clinically stable adults living with HIV to decrease the time on ART and reduce the number of viral load measurements could potentially reduce the burden faced by patients and health systems. However, implementing DSD earlier in patients' treatment may not provide them with the support needed to become stable in care and achieve viral suppression. Currently, different standards for clinical stability exist: while the WHO defines clinically stable PLWH as those on ART for 1 year with 2 consecutive suppressed viral loads,[2], other HIV programs in sub-Saharan Africa use shorter intervals (i.e. 6 months after ART initiation) and/or only require a single suppressed viral load for categorization as stable.[6–8] To date, no studies have empirically compared clinical outcomes of newly-diagnosed PLWH who transition to DSD

models after shorter intervals in care or fewer viral load measurements compared to the current standard of care.

We are therefore conducting this exploratory, unblinded, randomized controlled trial to examine the feasibility, acceptability, and preliminary efficacy of a less intensive DSD model. Specifically, the objectives of this study are to test the effect of 1) reducing the time to DSD from 12 to 6 months after ART initiation, and 2) reducing the number of suppressed viral load measurements required to enter DSD from two to one. To achieve these objectives, we are conducting a three arm, unblinded pilot intervention study. We hypothesize that: a) reducing the time to DSD from 12 to 6 months will be non-inferior to usual care with respect to viral suppression at 12 months; b) participants who enter DSD after one suppressed viral load will have non-inferior rates of viral suppression at 12 months compared to those who require two consecutive suppressed viral loads to enter DSD.

METHODS AND ANALYSIS

Trial design

This three-arm, unblinded, parallel group randomized controlled trial will examine the feasibility, acceptability and preliminary efficacy of reducing the time to DSD from 12 to 6 months as well as reducing from two to one the number of suppressed viral loads required to enter DSD, compared to usual care. The primary (viral suppression at 12 months after ART initiation) and secondary (appointment attendance over 12 months after ART initiation) efficacy outcomes will be compared using an exploratory, non-inferiority analysis.

Study setting

Rwanda, a landlocked nation with a population of nearly 13 million, became one of the first sub-Saharan African countries to implement Treat All nationally in 2016. The Rwandan HIV program has been successful, with recent estimates of >95% of PLWH on ART and viral suppression >90%.[3,9] Rwanda has a pyramidal health system, with 8 national referral hospitals, 36 district hospitals, and nearly 500 public health centers. Primary health care is predominantly delivered at health centers, which provide health promotion, preventive and treatment services in medicine, surgery, obstetrics and pediatrics, and are largely staffed by

nurses. HIV care in Rwanda is decentralized and provided at nearly all health centers, and includes diagnostic testing, chronic disease management, and ART.

This study will be carried out in three health facilities located in Rwanda's capital city, Kigali: Gikondo Health Center, Kicukiro Health Center, and Rwanda Military Hospital. Together, these health facilities provide primary HIV care to approximately 6,000 PLWH, including approximately 300 newly-diagnosed patients who enroll in care annually.

Eligibility

Inclusion criteria for this study are: 1) ≥15 years of age; 2) newly-diagnosed with HIV within prior 6 months; 3) enrolled in HIV care at a participating study health facility within prior 30 days; 4) initiated ART. Exclusion criteria are: 1) planning on moving away from Kigali area during 12-month duration of study; 2) pregnant at time of study enrollment; 3) co-infected with active tuberculosis at time of study enrollment; 4) concurrent known severe mental health or substance use disorder; 5) unable to provide informed consent.

Interventions

Participants will be randomized to one of three arms in a 1:1:1 ratio, as follows. *Arm 1: Entry into the DSD model at six months after enrollment in HIV care with one suppressed viral load*. In this arm, participants will have their viral loads measured at 5 months after enrollment in HIV care. If the viral load is suppressed, they will advance to a spaced out appointment schedule of clinical appointments every six months and ART pick up every three months. *Arm 2: Entry into the DSD model at six months after enrollment in HIV care with two suppressed viral loads*. In this arm, participants will have viral loads measured at 3 and 5 months after enrollment in HIV care. If both are suppressed, they will advance to a spaced-out appointment schedule of clinical appointments every six months and ART pick up every three months. *Arm 3: Usual care*. In this arm, participants will have their viral loads measured at 5 months, but will continue on an appointment schedule of clinical appointments every three months and ART pick up monthly.

For participants in the intervention arms, the decision to advance patients to a DSD schedule is primarily contingent on their viral load measurements at three and/or five months. Health care providers at the health facilities may determine that patients are not eligible for a spaced-out appointment schedule based on clinical assessment.

Before the study begins enrollment, staff at participating health facilities will receive training on the study protocol including eligibility criteria, study design and appointment schedules for the three arms. Throughout the study, the research team will regularly communicate with health facility staff to ensure that eligible study participants in the intervention arms advance to a spaced-out appointment schedule. The study team will review participant medical files to assess fidelity to the appointment schedule. While appointment schedules will be dictated by the study protocol, all other clinical treatments will be at the discretion of health facility clinicians. Following the trial, participants will continue in regular HIV care at their health facility.

Outcomes

To determine the preliminary efficacy of less frequent appointments and virologic monitoring on patient outcomes, we will measure viral suppression (primary efficacy outcome) and appointment attendance (secondary efficacy outcome). Viral suppression will be measured as the proportion of participants in each arm who achieve viral suppression (viral load <200 copies/ml) at 12 months after enrollment into HIV care. Appointment attendance will primarily be measured as the proportion of participants who attend all clinical visits over the first 12 months after ART initiation, by reviewing participant medical records; we will also measure this outcome as the overall proportion of scheduled visits attended.

Feasibility of an early spaced-out appointment schedule and less frequent virologic monitoring will be examined using process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measures. We will also conduct structured interviews with health facility staff at the end of the study to determine feasibility of implementing this intervention at a larger scale.

Acceptability of an early spaced-out appointment schedule and less frequent virologic monitoring will be measured through surveys of satisfaction with health care [10,11] as well as structured qualitative interviews with patients and health facility staff in all arms to understand attitudes towards and satisfaction with various appointment schedules, as well as a review of adverse event logs.

We will also measure the following:

- Changes in ART adherence will be collected by participant self-report at study entry, 6- and 12-months after ART initiation.

- Changes in participant quality of life will be measured by the EuroQOL-5 Dimension-5 Levels (EQ-5D-5L),[12] which measures self-rated problems in 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as self-rated health. We will collect and report changes in quality of life at study entry, 6- and 12-months after ART initiation.
- Changes in enacted, internalized, and anticipated stigma will be measured using a modified version of the HIV stigma scale [10] as well as the HIV/AIDS Stigma Instrument-PLWA (HASI-P) Scale.[13] We will measure stigma at study entry, 6- and 12-months after ART initiation.
- Changes in participant health-related expenditures will be measured at study entry, 6- and 12-months after ART initiation.

STUDY PROCEDURES

Recruitment

Active recruitment will occur via health facility nurses who will inform potentially eligible patients about the study during their routine appointments. Each week a designated health facility staff member will provide the research assistant with a list of patients who indicated interest in participating. Passive recruitment will occur through research assistants who will also make general announcements about the study during morning health education sessions at health facilities, and be available to answer questions and collect interested patient's contact information. Interested patients will be screened for eligibility, and if eligible will be offered enrollment in the study.

Study timeline

The study enrollment visit will occur within 30 days of the patient's enrollment in HIV care. All participants will have additional research visits six and twelve months after enrolling in HIV care. Research visits will entail participant interviews and medical record review. Participants will also visit the health facility for viral load measurements at three and five months after enrolling HIV care, depending on the study arm. **TABLE 1** describes the schedule of research visits and data assessments.

TABLE 1. Schedule of enrollment, interventions, and assessments.

		STUDY PERIOD													
	ART initiation	STUDY ENTRY	Allocation	Post-allocation											Close-out
TIMEPOINT (Month)	**0**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
ENROLMENT:															
Eligibility screen		●													
Informed consent		●													
Allocation			●												
INTERVENTION: appointment and VL schedule															
Arm 1 (Early DSD after one suppressed VL)															
Clinical appointments						●			●						●
ART pick-up				●	●	●	●	●	●			●			●
Viral load measurement						●		●							●
Arm 2 (Early DSD after two suppressed VLs)															
Clinical appointments						●			●						●
ART pick-up				●	●	●	●	●	●			●			●
Viral load measurement								●							●
Arm 3 (Usual care)															
Clinical appointments						●			●			●			●
ART pick-up				●	●	●	●	●	●	●	●	●	●	●	●
Viral load measurement								●							●
RESEARCH VISITS (All arms)				●					●						●
ASSESSMENTS:															
Outcomes															
Viral suppression															●
Appointment and ART pick-up adherence															●
Acceptability of appointment schedules[11,12]															●
Feasibility															●
Baseline variables															
Demographic information				●											
HIV care				●											
ART adherence				●					●						●
Quality of life[10]				●					●						●
Stigma measurements[11,13]				●					●						●
Patient costs				●					●						●

At the conclusion of the study enrollment visit, the research assistant will give the participant a reminder card with the date of the next research visit. Study staff will call the participant one week and one day before the scheduled research visits to remind them of the appointment date and time. Participants who do not appear for scheduled research visits will be called and visits rescheduled within 14 days. Research staff will not provide reminders for clinical or pharmacy visits.

Informed consent

Newly-diagnosed PLWH who have enrolled in care within 30 days and meet eligibility criteria will be referred to the study team. At study entry, written, informed consent to participate will be obtained from all participants or their parent or legal guardian. No additional consent provisions are required for collection and use of participant medical record data and biological specimens in this study.

Randomization

At study entry, participants will be randomized to one of three study arms. To ensure equal distribution of key factors among randomization arms, we will stratify randomization by age group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure comparison groups of approximately equal size. Randomization will be computer generated, occur in blocks of 6 with 1:1:1 allocation across study arms.

To ensure concealment of allocation, a centrally-located data manager will generate the allocation sequence and store the sequence in a password-protected file. Since the intervention is not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The allocation sequence will be generated using SAS (9.4). Upon enrollment in the study, research staff will use the randomization function in REDCap (Research Electronic Data Capture, v10.0.16, 2020, Vanderbilt University) to assign participants to study arms. Because this study is testing the effect of different appointment schedules, it is not feasible to blind participants or study personnel, and thus allocation will not be concealed from staff or participants.

Data collection

Data will be collected through participant interviews, laboratory tests and medical record review. Research staff will be trained in systematic data collection by interview. Interviews will be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime protocols will be implemented in the event of internet outage. Medical records will be reviewed at the end of every study visit, with data entered directly into REDCap. Blood specimens for clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several subsequent visits during the study, and results reported to participants and to clinical staff at health facilities. No genetic or molecular analyses will be performed; specimens will not be stored for future use.

Analytic approach

We expect to enroll 90 participants into this study. This pilot study is designed to test acceptability, feasibility and preliminary efficacy, and is thus not powered for hypothesis testing. Sample size was determined based on available resources for conducting the study. The primary analyses will be by intention to treat.

Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the data, examining frequencies, means, medians and ranges to identify any systematic or logical errors. As this is a pilot, exploratory study, analyses will be descriptive in nature. Validated instruments will be coded according to respective scoring instructions. Feasibility will be examined using descriptive analyses to describe process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measurements. We will also conduct thematic analysis of qualitative, structured interviews to determine intervention acceptability of less intensive DSD models as well as feasibility of implementing this intervention at a larger scale.

For the preliminary efficacy outcome of viral suppression, we will first compare proportions of patients achieving viral suppression and attending all appointment/pharmacy visits using chi-square tests. We will then 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. Intervention arms will be considered non-inferior to usual care if the lower margin of the 95% confidence interval of the difference between risk ratios does not extend more than 10% below the equivalence point, based on an expected 90% viral suppression rate in the control arm

(3). Because of the small number of participants we anticipate enrolling in this pilot study, we may not be sufficiently powered to detect 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.

Due to the pilot nature of this study, relatively short duration, and small planned enrollment size, we do not plan on conducting interim analyses or subgroup analyses. Data will be analyzed using an intention-to-treat approach. We will not impute missing data.

Data management

In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g. range checks, logical dates) and store interview, medical record and laboratory data. No identifying information will be collected in REDCap. Only research investigators and staff will have access to study databases. Data quality will be promoted through training research staff to uniformly collect and enter data and by periodic data quality monitoring.

Confidentiality

The following measures will be utilized to protect participant confidentiality: All paper study records (i.e. informed consent documents) will be kept in locked file cabinets with access limited to study staff. In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap data will not include any name-based or identifying information. Study databases will be maintained on encrypted, password-protected computers and servers to which only study staff will have access. To prevent linking of sensitive material to participants' personal identifiers, we will utilize separate "name-based" and "ID-based" systems. For any paper forms, all documents that have patient identifiers (e.g. consent forms, locator 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. There will only be one electronic document that

links participants' names to their study IDs, stored on a local, password-protected, encrypted server. Publication or presentation of study results will not identify subjects.

Study oversight

This is a pilot study of approximately 90 participants being conducted to test feasibility, acceptability and preliminary efficacy of a modified appointment schedule. This is a low risk study that involves pilot testing an intervention that will enroll a relatively small number of participants, and it is unlikely that study participants will experience adverse reactions related to study participation. Therefore there will not be a Data Safety and Monitoring Board. The study team, consisting of the PI, co-investigators, and research staff, meet weekly to review study progress, including review of adverse events. If adverse events occur, the PI will act to minimize their impact and ensure the adverse event is reported to the responsible authorities in a timely manner as required. There is no coordinating center or steering committee. This pilot trial will not be audited.

Adverse event reporting and harms

The PI, together with the study team, will be responsible for regularly monitoring data and safety, specifically assessing for adverse events and breach of confidentiality. If adverse events occur, the study team will: 1) identify the concern, 2) activate the appropriate response to minimize the adverse event, and 3) ensure the adverse event is reported to the responsible authority in a timely manner. If patients have a medical or psychiatric decompensation during the study, research staff will inform their direct supervisor, who will assess the patient in-person, and will notify the PI or co-investigators immediately. Based on clinical judgment, study participants will be referred to psychiatric or medical consultation in the health facility or referred for emergency care. The study database will be secured with encryption and password protection, and the study team will monitor the database for potential breaches of confidentiality.

All adverse events will be compiled monthly. Unanticipated, non-serious adverse events will be documented and reported by the PI to the Albert Einstein College of Medicine IRB and the Rwanda National Ethics Committee within 30 days. Serious adverse events will be reported by the PI to the Albert Einstein College of Medicine IRB and Rwanda National Ethics Committee within 48 hours by phone, email, or fax.

Discussion

This exploratory trial will pilot test reducing the time to DSD from 18 to 6 months as well as reducing the number of suppressed viral loads required to enter DSD from two to one, compared to usual care. If found feasible, acceptable, and efficacious, this approach could reduce inconvenience and stigma for newly-diagnosed PLWH as well as lower the medical resources required for treatment.

This study may face potential limitations. Participants in the intervention arm with two viral load measurements effectively have twice as many opportunities to not be virally suppressed, and therefore may be less likely to advance to DSD. Similarly, participants will advance to DSD at the discretion of treating clinicians. This may bias the study findings if participants in the intervention arms effectively follow the standard of care, and may result in less power to detect differences between the study arms in our intention to treat analysis. Nonetheless, the study will provide important feasibility and acceptability data on the optimal number of viral load measurements needed to determine clinical stability. Blinding will not be feasible for this study, which may bias the study findings. Finally, we will be enrolling patients who receive care at health facilities located in or near the capital of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa. This may limit the generalizability of our findings.

DSD models, including less frequent appointment schedules, are increasingly being adopted across HIV care settings globally, and are acceptable to patients and cost-effective.[14–16] A key question in implementing DSD models is determining at what point patients receiving HIV care can be considered clinically stable. By testing the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally.

Patient and public involvement

The design of this study was informed by findings of formative, qualitative research conducted with patients at study health centers,[5] clinical experiences of several of the authors, along with input from public health and clinical leaders in Rwanda. The research questions and design were reviewed by investigators with expertise in HIV health services delivery and

infectious diseases, along with input from an advisory committee consisting of leadership from study health centers as well as the Rwanda Biomedical Center, the nation's central health implementation agency.

ETHICS AND DISSEMINATION

This clinical trial was approved by the institutional review board (IRB) of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee and is registered on www.clinicaltrials.gov [NCT04567693].

By testing the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally. We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to patients, providers and key institutional stakeholders. Study findings will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) standards.

TRIAL STATUS

The current protocol is version 1.4, dated 28 September 2020. Any important protocol amendments will be communicated immediately to the responsible ethical committees and will be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is expected to continue until August 2021, with follow-up continuing until August 2022.

AUTHOR'S CONTRIBUTIONS

JR is the Principal Investigator; he conceived the study, led the proposal and protocol development. SH, CI, FM, AM, BM, GM, and KA contributed to study design and to development of the proposal. ER, DSH, PM, and MY provided additional input to study design. CZ provided statistical support. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests or conflicts of interest to disclose.

DATA AVAILABILITY

The final trial dataset will not be released publicly based on policies of the Rwandan Ministry of Health. In August 2023 (two years after the conclusion of data collection), the dataset can be shared on upon written request to, and after review and approval by, Dr. Gad Murenzi (gadcollins@gmail.com).

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SPIRIT CHECKLIST

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 6
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	15, 16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6,7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8, 11, 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking)	10

		should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8,11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6,7
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for a pilot, unblinded randomized control study.

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Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for a pilot, unblinded randomized control study.

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ABSTRACT

Introduction: Current HIV guidelines recommend differentiated service delivery (DSD) models that allow for fewer health center visits for clinically stable people living with HIV (PLHIV). Newly-diagnosed PLHIV may require more intensive care early in their treatment course, yet frequent appointments can be burdensome to patients and health systems. Determining the optimal parameters for defining clinical stability and transitioning to less frequent appointments could decrease patient burden and health system costs. The objectives of this pilot study are to explore the feasibility and acceptability of: 1) reducing the time to DSD from 12 to 6 months after antiretroviral therapy (ART) initiation, and 2) reducing the number of suppressed viral loads required to enter DSD from two to one.

Methods and analyses: The present study is a pilot, unblinded trial taking place in three health facilities in Kigali, Rwanda. Current Rwandan guidelines require PLHIV to be on ART for ≥12 months with two consecutive suppressed viral loads in order to transition to less frequent appointments. We will randomize 90 participants to one of three arms: entry into DSD at six months after one suppressed viral load (N=30), entry into DSD at six months after two suppressed viral loads (N=30), or current standard of care (N=30). We will measure feasibility and acceptability of this intervention; clinical outcomes include viral suppression at 12 months (primary outcome) and appointment attendance (secondary outcome).

Ethics and dissemination: This clinical trial was approved by the institutional review board of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee. Findings will be disseminated through conferences and peer-reviewed publications as well as meetings with stakeholders.

Trial registration: Clinicaltrials.gov [NCT04567693]

Strengths and limitations of this study

- A randomized, controlled trial examining clinical outcomes of newly-diagnosed people living with HIV who transition to differentiated service delivery models after shorter intervals in care or fewer viral load measurements will provide important evidence to inform HIV program implementation in Rwanda as well as globally.
- A three-armed study will be able to simultaneously explore the impact of: 1) reducing the time to differentiated service delivery from 12 to 6 months after antiretroviral therapy initiation, and 2) reducing the number of suppressed viral load measurements required to enter differentiated service delivery from two to one.
- Consideration of experienced and anticipated stigma as well as patient expenditures will provide additional information on the feasibility and acceptability of this model of care.
- The unblinded nature of this trial may lead to bias in subsequent clinical management and outcome ascertainment.
- The setting of the trial (urban health facilities in the capitol city of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa) may limit the generalizability of our findings.

INTRODUCTION

With the goal of ending the pandemic, the UNAIDS "90-90-90" targets for 2020 are that 90% of all people living with HIV (PLHIV) know their HIV status, 90% of people with diagnosed HIV infection receive sustained antiretroviral therapy (ART), and 90% of all people receiving ART achieve viral suppression. [1] To this end, in 2015 the World Health Organization (WHO) recommended in its Treat All guidelines that all PLHIV initiate ART as quickly as possible after diagnosis.[2] Since implementation of its Treat All policy in 2016, Rwanda has nearly achieved UNAIDS 90-90-90 targets,[3] yet groups including men and younger PLHIV remain at higher risk of poorer outcomes. Reducing barriers to initiating and adhering to therapy is thus paramount to ensuring all PLHIV in Rwanda succeed in HIV therapy.

The 2016 WHO guidelines recommend differentiated service delivery (DSD) models as a strategy to manage diverse sets of patient needs.[2] Under these guidelines, PLHIV considered to be clinically stable – on ART for 1 year with 2 consecutive suppressed viral loads – can be seen less frequently for clinical assessments and dispensed ART for longer periods. Such approaches are feasible, acceptable, and achieve equivalent or improved retention in care and viral suppression.[4-8] To date, numerous countries in sub-Saharan Africa have adopted DSD models,[9] and some have modified eligibility for these programs in response to the Covid-19 pandemic as a means to promote social distancing.[10] While most DSD programs limit eligibility to patients who are clinically stable, heterogeneity exists with respect to definitions of stability. Some programs in sub-Saharan Africa use shorter intervals (i.e. 6 months after ART initiation) and/or only require a single suppressed viral load for categorization as stable.[9,11-13] To date, most studies of DSD models have been limited to clinically stable patients, and no studies have empirically compared clinical outcomes of newly-diagnosed PLHIV who transition to DSD models after shorter intervals in care or fewer viral load measurements compared to the current standard of care.

To optimize HIV program outcomes under Treat All, Rwanda simultaneously introduced differentiated service delivery (DSD) models to align services with the variable needs and preferences of different groups of PLHIV. [14] Stable PLHIV - adults on first- or second-line ART for ≥12 months with two consecutive suppressed viral loads - can collect ART every 3 months (rather than monthly) and attend clinical appointments every 3 or 6 months based on clinical criteria (**Table 1**). Individuals in the unstable category – including newly diagnosed

PLHIV (<12 months on ART), women who are pregnant or lactating, patients with concurrent mental health disorders, and PLHIV who are not virally suppressed – must visit clinic monthly for ART collection and adherence assessment.

Our earlier research in Rwanda identified frequent appointments as burdensome to newly-diagnosed PLHIV because of structural issues such as transportation cost and long wait times, as well as stigma experienced while traveling to and while at the health center.[15] Modifying the definition of clinically stable adults living with HIV to decrease the time on ART and reduce the number of viral load measurements could potentially reduce the burden faced by patients and health systems. However, implementing DSD earlier in patients' treatment may not provide them with the support needed to become stable in care and achieve viral suppression.

We are therefore conducting a pilot, unblinded, three-arm randomized controlled trial to explore the impact of two less intensive DSD models: 1) reducing the time to DSD from 12 to 6 months after ART initiation, and 2) reducing the number of suppressed viral load measurements required to enter DSD from two to one. Our objectives are to understand whether these less-intensive DSD models are acceptable to participants and stakeholders, determine whether their implementation is feasible in the context of current Rwandan HIV guidelines, and obtain parameter estimates to guide future efficacy testing. This study will contribute relevant information and actionable information to inform DSD care delivery in Rwanda and help plan for a future, fully-powered study to test these models.

TABLE 1. Current differentiated care delivery model in Rwanda

	Standard of care	Differentiated Service Delivery	
	Unstable	**Stable A**	**Stable B**
Patient	• Patients on ART for <12 months • Severe mental health disorder • Pregnant or lactating • On ART but not virally suppressed • Patients on 3rd line ART • Children <2 years old	• Adults on 1st and 2nd line ART with 2 consecutive suppressed viral loads	• Children ≥2 years • Adolescents • Key populations • Co-infected with TB or hepatitis
Provider	Clinical nurse		
Service location	Health center		
Frequency of clinical visits	Every 3 months	Every 6 months	Every 3 months
Frequency of ART pick-up	Monthly	Every 3 months	Every 3 months

ART: antiretroviral therapy; TB: tuberculosis

METHODS AND ANALYSIS

Trial design

This three-arm, unblinded, parallel group randomized controlled trial will examine the feasibility and acceptability of reducing the time to DSD from 12 to 6 months as well as reducing from two to one the number of suppressed viral loads required to enter DSD, compared to usual care. The primary (viral suppression at 12 months after ART initiation) and secondary (appointment attendance over 12 months after ART initiation) efficacy outcomes will be compared using an exploratory, non-inferiority analysis.

Study setting

Rwanda, a landlocked nation with a population of nearly 13 million, became one of the first sub-Saharan African countries to implement Treat All nationally in 2016. The Rwandan HIV program has been successful, with recent estimates of >95% of PLHIV on ART and viral suppression >90%.[3,16] Rwanda has a pyramidal health system, with 8 national referral hospitals, 36 district hospitals, and nearly 500 public health centers. Primary health care is predominantly delivered at health centers, which provide health promotion, preventive and treatment services in medicine, surgery, obstetrics and pediatrics, and are largely staffed by nurses. HIV care in Rwanda is decentralized and provided at nearly all health centers, and includes diagnostic testing, chronic disease management, and ART. Current guidelines in Rwanda specify that all newly-diagnosed patients should be on one of two ART regimens: tenofovir disoproxil fumarate, lamivudine and dolutegravir, or abacavir, lamivudine and dolutegravir.[17]

This study will be carried out in three health facilities located in Rwanda's capital city, Kigali: Gikondo Health Center, Kicukiro Health Center, and Remera Health Center. Together, these health facilities provide primary HIV care to approximately 6,000 PLHIV, including approximately 300 newly-diagnosed patients who enroll in care annually.

Eligibility

Inclusion criteria for this study are: 1) ≥15 years of age; 2) newly-diagnosed with HIV within prior 6 months; 3) enrolled in HIV care at a participating study health facility within prior 30 days; 4) initiated ART. Exclusion criteria are: 1) planning on moving away from Kigali area

during 12-month duration of study; 2) pregnant or lactating at time of study enrollment; 3) co-infected with active tuberculosis at time of study enrollment; 4) concurrent known severe mental health or substance use disorder; 5) unable to provide informed consent.

Interventions

Participants will be randomized within 1 month of ART initiation to one of three arms in a 1:1:1 ratio, as follows. *Arm 1: Entry into the DSD model at six months after ART initiation with one suppressed viral load*. In this arm, participants will have their viral loads measured at 5 months after ART initiation. If the viral load is suppressed, they will advance to a spaced out appointment schedule of clinical appointments every six months and ART pick up every three months. *Arm 2: Entry into the DSD model at six months after ART initiation with two suppressed viral loads*. In this arm, participants will have viral loads measured at 3 and 5 months after ART initiation. If both are suppressed, they will advance to a spaced-out appointment schedule of clinical appointments every six months and ART pick up every three months. Because patients are expected to be on a dolutegravir-based regimen, we anticipate that those adherent to ART will have achieved viral suppression within 3 months of ART initiation. *Arm 3: Usual care*. In this arm, participants will have their viral loads measured at 5 months, but will continue on an appointment schedule of clinical appointments every three months and ART pick up monthly.

For participants in the intervention arms, the decision to advance patients to a DSD schedule is primarily contingent on their viral load measurements at three and/or five months. Health care providers at the health facilities may determine that patients are not eligible for a spaced-out appointment schedule based on clinical assessment. For example, individuals randomized to one of the intervention arms, but who subsequently become ineligible for a DSD schedule because of pregnancy will not be permitted to continue in the DSD schedule and will cross to the usual care arm. Participants in the usual care arm will not be eligible for advancement to a DSD schedule until the study ends, however, those in the intervention arms may choose to attend appointments more frequently if agreed to by their clinician.

Before the study begins enrollment, staff at participating health facilities will receive training on the study protocol including eligibility criteria, study design and appointment schedules for the three arms. Throughout the study, the research team will regularly communicate with health facility staff to ensure that eligible study participants in the intervention arms advance to a

spaced-out appointment schedule. The study team will review participant medical files to assess fidelity to the appointment schedule. While appointment schedules will be dictated by the study protocol, all other clinical treatments will be at the discretion of health facility clinicians. Following the trial, participants will continue in regular HIV care at their health facility.

Outcomes

To explore the impact of less frequent appointments and virologic monitoring on patient outcomes, we will measure viral suppression (primary efficacy outcome) and appointment attendance (secondary efficacy outcome). Viral suppression will be measured as the proportion of participants in each arm who achieve viral suppression (viral load <200 copies/ml, based on current Rwandan guidelines) at 12 months after ART initiation. Appointment attendance will primarily be measured as the proportion of participants who attend all clinical visits over the first 12 months after ART initiation, by reviewing participant medical records; we will also measure this outcome as the overall proportion of scheduled visits attended. Patients at study health centers who do not attend a scheduled appointment are called the next day to reschedule. If unsuccessful, appointments are considered missed; however, outreach efforts continue to be made.

Feasibility of an early spaced-out appointment schedule and less frequent virologic monitoring will also be examined using process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measures. We will also conduct structured interviews with health facility staff at the end of the study to determine feasibility of implementing this intervention at a larger scale.

Acceptability of an early spaced-out appointment schedule and less frequent virologic monitoring will be measured through surveys of satisfaction with health care [18,19] as well as structured qualitative interviews with patients and health facility staff in all arms to understand attitudes towards and satisfaction with various appointment schedules, as well as a review of adverse event logs.

We will also measure the following tertiary outcomes:

- Changes in ART adherence will be collected using 7- and 30-day self-reported ART adherence measures at study entry, 6- and 12-months after ART initiation.

- Changes in participant quality of life will be measured by the EuroQOL-5 Dimension-5 Levels (EQ-5D-5L),[20] which measures self-rated problems in 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as self-rated health. We will collect and report changes in quality of life at study entry, 6- and 12-months after ART initiation.
- Changes in enacted, internalized, and anticipated stigma will be measured using a modified version of the HIV stigma scale [19] as well as the HIV/AIDS Stigma Instrument-PLWA (HASI-P) Scale.[21] We will measure stigma at study entry, 6- and 12-months after ART initiation.
- Changes in participant health-related expenditures will be measured at study entry, 6- and 12-months after ART initiation.

STUDY PROCEDURES

Recruitment

Active recruitment will occur via health facility nurses who will inform potentially eligible patients about the study during their routine appointments. Each week a designated health facility staff member will provide the research assistant with a list of patients who indicated interest in participating and who meet eligibility criteria (i.e. newly-diagnosed, not pregnant or lactating, without severe mental health conditions). Passive recruitment will occur through research assistants who will also make general announcements about the study during morning health education sessions at health facilities, and be available to answer questions and collect interested patient's contact information. Interested patients will be screened by study staff for eligibility, and if eligible will be offered enrollment in the study.

Study timeline

The study enrollment visit will occur within 30 days of the patient's enrollment in HIV care at the health center. All participants will have additional research visits six and twelve months after enrolling in HIV care. Research visits will entail participant interviews and medical record review. Participants will also visit the health facility for viral load measurements at three and five months after ART initiation, depending on the study arm. Participants will be reimbursed for all research and viral load visits. **Table 2** describes the schedule of clinical and research visits. At

the conclusion of the study enrollment visit, the research assistant will give the participant a reminder card with the date of the next research visit. Study staff will call the participant one week and one day before the scheduled research visits to remind them of the appointment date and time. Participants who do not appear for scheduled research visits will be called and visits rescheduled within 14 days. Research staff will not provide reminders for clinical or pharmacy visits.

TABLE 2. Schedule of health center and research visits.

	Health center and research visits after ART initiation (months)											
TIMEPOINT (Month)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
INTERVENTION: appointment and viral load schedule												
Arm 1 (Early DSD after one suppressed viral load)												
Clinical appointments			●			●						●
ART pick-up	●	●	●	●	●	●			●			●
Viral load measurement					●							●
Arm 2 (Early DSD after two suppressed viral loads)												
Clinical appointments			●			●						●
ART pick-up	●	●	●	●	●	●			●			●
Viral load measurement			●		●							●
Arm 3 (Usual care)												
Clinical appointments			●			●			●			●
ART pick-up	●	●	●	●	●	●	●	●	●	●	●	●
Viral load measurement					●							●
RESEARCH VISITS (All arms)	●					●						●

ART: antiretroviral therapy; DSD: differentiated care delivery

Informed consent

Newly-diagnosed PLHIV who have enrolled in care within 30 days and meet eligibility criteria will be referred to the study team. At study entry, written, informed consent to participate will be obtained from all participants (Supplemental File 1). Participants aged 15-18 will provide assent with informed consent obtained from their parent or legal guardian. Research staff will read the informed consent document to participants in its entirety; participants unable to sign their name will be permitted to sign with an "X." No additional consent provisions are required for collection and use of participant medical record data and biological specimens in this study.

Randomization

At study entry, participants will be randomized to one of three study arms. To ensure equal distribution of key factors among randomization arms, we will stratify randomization by age group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure comparison groups of approximately equal size. Randomization will be computer generated, occur in blocks of 6 with 1:1:1 allocation across study arms.

To ensure concealment of allocation, a centrally-located data manager will generate the allocation sequence and store the sequence in a password-protected file. Since the intervention is not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The allocation sequence will be generated using the Proc Plan function in SAS (9.4). Upon enrollment in the study, research staff will use the randomization function in REDCap (Research Electronic Data Capture, v10.0.16, 2020, Vanderbilt University) to assign participants to study arms. Because this study is testing the effect of different appointment schedules, it is not feasible to blind participants or study personnel, and thus allocation will not be concealed from staff or participants.

Data collection

Data will be collected through participant interviews, laboratory tests and medical record review. Research staff will be trained in systematic data collection by interview. Interviews will be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime protocols will be implemented in the event of internet outage. Medical records will be reviewed at the end of every study visit, with data entered directly into REDCap. Venous blood specimens for clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several subsequent visits during the study. Results will be provided to clinical staff at health facilities, who will input them into the medical record and report them to participants, consistent with routine clinical practices. Viral load measurements will be performed using the Abbott Allinity m instrument, with a lower limit of detection of 20 copies/ml. No genetic or molecular analyses will be performed; specimens will not be stored for future use.

Analytic approach

We expect to enroll 90 participants into this study. This pilot study is designed to test feasibility and acceptability and is thus not powered for hypothesis testing. Sample size was

determined based on available resources for conducting the study. The primary analyses will be by intention to treat.

Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the data, examining frequencies, means, medians and ranges to identify any systematic or logical errors. As this is a pilot study, analyses will be descriptive in nature. Validated instruments will be coded according to respective scoring instructions. Feasibility will be examined using descriptive analyses to describe process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measurements. We will also conduct thematic analysis of qualitative, structured interviews to determine intervention acceptability of less intensive DSD models as well as feasibility of implementing this intervention at a larger scale.

For the outcomes of viral suppression and appointment adherence, the primary analysis will be intention to treat including all randomized participants, with those who are missing outcome data considered treatment failures. We will first compare study arms with respect to the proportions of patients achieving viral suppression and attending all clinical and pharmacy visits using chi-square tests. We will then use logistic regression to estimate odds ratios and associated 95% confidence intervals for the effect of each intervention arm compared to the control, adjusting for key baseline covariates that are imbalanced between groups. Because of the small number of participants we anticipate enrolling in this pilot study, we will not be sufficiently powered to detect statistically significant differences in outcomes. However, the findings obtained from this study will provide key results on intervention feasibility and guide a future, larger study to test intervention efficacy.

Due to the pilot nature of this study, relatively short duration, and small planned enrollment size, we do not plan on conducting interim analyses. In secondary analyses, we will examine outcomes of viral suppression and appointment attendance using a per-protocol approach, We will also compare statistical results using a dataset with imputed values and the dataset that drops missing values, guiding our interpretation of the impact of missing data on findings, as well as our interpretation of overall results. Additional sub-analyses will examine outcomes separately among subgroups of interest (i.e. men, young patients, early defaulters).

Data management

In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g. range checks, logical dates) and store interview, medical record and laboratory data. No identifying information will be collected in REDCap. Only research investigators and staff will have access to study databases. Data quality will be promoted through training research staff to uniformly collect and enter data and by periodic data quality monitoring.

Confidentiality

The following measures will be utilized to protect participant confidentiality: All paper study records (i.e. informed consent documents) will be kept in locked file cabinets with access limited to study staff. In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap data will not include any name-based or identifying information. Study databases will be maintained on encrypted, password-protected computers and servers to which only study staff will have access. To prevent linking of sensitive material to participants' personal identifiers, we will utilize separate "name-based" and "ID-based" systems. For any paper forms, all documents that have patient identifiers (e.g. consent forms, locator forms) will be filed together. Any files that do not include identifying information or signatures will only use participants' unique, study-specific IDs (rather than names) and will be filed separately from name-based documents. There will only be one electronic document that links participants' names to their study IDs, stored on a local, password-protected, encrypted server. Publication or presentation of study results will not identify subjects.

Study oversight

This is a pilot study of approximately 90 participants being conducted to test feasibility and acceptability of a modified appointment schedule. This is a low risk study that involves pilot testing an intervention that will enroll a relatively small number of participants, and it is unlikely that study participants will experience adverse reactions related to study participation. Therefore there will not be a Data Safety and Monitoring Board. The study team, consisting of the PI, co-

investigators, and research staff, meet weekly to review study progress, including review of adverse events. If adverse events occur, the PI will act to minimize their impact and ensure the adverse event is reported to the responsible authorities in a timely manner as required. There is no coordinating center or steering committee. This pilot trial will not be audited.

Adverse event reporting and harms

The PI, together with the study team, will be responsible for regularly monitoring data and safety, specifically assessing for adverse events and breach of confidentiality. If adverse events occur, the study team will: 1) identify the concern, 2) activate the appropriate response to minimize the adverse event, and 3) ensure the adverse event is reported to the responsible authority in a timely manner. If patients have a medical or psychiatric decompensation during the study, research staff will inform their direct supervisor, who will assess the patient in-person, and will notify the PI or co-investigators immediately. Based on clinical judgment, study participants will be referred to psychiatric or medical consultation in the health facility or referred for emergency care. The study database will be secured with encryption and password protection, and the study team will monitor the database for potential breaches of confidentiality.

All adverse events will be compiled monthly. Unanticipated, non-serious adverse events will be documented and reported by the PI to the Albert Einstein College of Medicine IRB and the Rwanda National Ethics Committee within 30 days. Serious adverse events will be reported by the PI to the Albert Einstein College of Medicine IRB and Rwanda National Ethics Committee within 48 hours by phone, email, or fax.

Discussion

This trial will pilot test reducing the time to DSD from 12 to 6 months as well as reducing the number of suppressed viral loads required to enter DSD from two to one, compared to usual care. If found feasible and acceptable, this approach could reduce inconvenience and stigma for newly-diagnosed PLHIV as well as lower the medical resources required for treatment.

This study may face potential limitations. Participants in the intervention arm with two viral load measurements effectively have twice as many opportunities to not be virally suppressed, and therefore may be less likely to advance to DSD. Similarly, participants will advance to DSD at the discretion of treating clinicians. This may bias the study findings if participants in the

intervention arms effectively follow the standard of care, and may result in less power to detect differences between the study arms in the intention to treat analysis. Nonetheless, the study will provide important feasibility and acceptability data on the optimal number of viral load measurements needed to determine clinical stability. Blinding will not be feasible for this study, which may bias the study findings. Finally, we will be enrolling patients who receive care at health facilities located in or near the capital of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa. This may limit the generalizability of our findings.

DSD models, including less frequent appointment schedules, are increasingly being adopted across HIV care settings globally, and are acceptable to patients and cost-effective.[4-8, 22-23] A key question in implementing DSD models is determining at what point patients receiving HIV care can be considered clinically stable. By testing the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally.

Patient and public involvement

The design of this study was informed by findings of formative, qualitative research conducted with patients at study health centers,[15] clinical experiences of several of the authors, along with input from public health and clinical leaders in Rwanda. The research questions and design were reviewed by investigators with expertise in HIV health services delivery and infectious diseases, along with input from an advisory committee consisting of leadership from study health centers as well as the Rwanda Biomedical Center, the nation's central health implementation agency.

ETHICS AND DISSEMINATION

This clinical trial was approved by the institutional review board (IRB) of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee and is registered on www.clinicaltrials.gov [NCT04567693].

By testing the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally. We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to patients, providers and key institutional stakeholders. Study findings will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) standards.

TRIAL STATUS

The current protocol is version 1.4, dated 28 September 2020. Any important protocol amendments will be communicated immediately to the responsible ethical committees and will be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is expected to continue until August 2021, with follow-up continuing until August 2022.

AUTHOR'S CONTRIBUTIONS

JR is the Principal Investigator; he conceived the study, led the proposal and protocol development. SH, CI, FU, AM, BM, GM, and KA contributed to study design and to development of the proposal. ER, DSH, PM, and MY provided additional input to study design. CZ provided statistical support. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests or conflicts of interest to disclose.

DATA AVAILABILITY

The final trial dataset will not be released publicly based on policies of the Rwandan Ministry of Health. In August 2024 (two years after the conclusion of data collection), the dataset can be shared on upon written request to, and after review and approval by, Dr. Gad Murenzi (gadcollins@gmail.com).

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KEY INFORMATION FOR *REDUCING TIME TO SPACED-OUT APPOINTMENTS FOR NEWLY-DIAGNOSED PEOPLE LIVING WITH HIV*

We are asking you to choose whether or not to volunteer for a research study about the best way to schedule appointments for people who are newly diagnosed with HIV. This page is designed to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn whether an appointment schedule with fewer appointments will make it easier for patients living with HIV to get their care. We will compare different appointment schedules to understand the costs and benefits of each one. Your participation in this research will last about 1 year.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You will not receive any direct benefit from participating in this study. However, some participants appreciate knowing they have contributed to research that may benefit others in the future.

For a complete description of benefits, refer to the Consent Document below.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may not want to participate in this study if you are worried about keeping your information absolutely private. In addition, sometimes answering questions about your health can be stressful.

For a complete description of alternate treatment/procedures, refer to the Consent Document below.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights or access to care you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The persons in charge of the study are Dr. Gad Murenzi (Rwanda) and Dr. Jonathan Ross (US) If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is:.

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

If you are a parent or legal guardian of a child who may take part in this study, permission from you and the assent (agreement) of your child may be required. When the word "you(r)" / "my" / "me" / "I" appears in this consent form, we mean the participant (you or your child); "we" means the research study doctors and research staff.

Introduction

You are being asked to participate in a research study called ***REDUCING TIME TO SPACED-OUT APPOINTMENTS FOR NEWLY-DIAGNOSED PEOPLE LIVING WITH HIV*.** Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no", your decision will not affect any of your rights or benefits or your access to care.

Why is this study being done?

The goal of this study is to understand whether there are benefits or harms from having less frequent appointments for HIV care starting at 6 months after diagnosis. Right now, people living with HIV in Rwanda must come to appointments often for the first 12 months after diagnosis, which can be difficult. We want to test whether having patients come less frequently will have an effect on patients' adherence to medication or appointments. We think that coming less frequently will not lead to worse adherence.

Why am I being asked to participate?

You are being asked to participate in this study because you are a person living with HIV, are at least 15 years old and are receiving health care from one of the health centers participating in the study. You are being asked to take part because you heard about the study from someone who works at the health center or from the research staff. In total, we expect approximately 90 people from 3 health facilities to take part in this study.

What will happen if I participate in the study?

If you choose to participate, you will be randomized to one of three appointment schedules. Randomization is like a coin flip. We do not control which schedule you will be assigned. The entire study will last for 1 year. In all schedules, you will continue to come to the health center until 6 months have passed since you first enrolled in care.

- In the first schedule, you will have a viral load checked two times between now and the 6-month point. If both viral loads are suppressed, then you will be scheduled to see the nurse every 6 months and come to the pharmacy for medication pick-up every 3 months.
- In the second schedule, you will have a viral load checked once between now and the 6-month point. If the viral load is suppressed, then you will be scheduled to see the nurse every 6 months and come to the pharmacy for medication pick-up every 3 months.
- In the third schedule, you will continue to come to the health center every 3 months to see the nurse and every month to the pharmacy for the entire study period.

As part of this study we will measure a few blood tests at the first and last research visits. These tests are the same tests that you would have done at the health center. To obtain the blood sample, we will wipe the skin on your arm with alcohol to clean it. Then, we will insert a small needle into a vein. Three tubes of blood will be drawn, about 20ml.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

As part of this study we will review your medical records and put the information we collect in our research records.

How many people will take part in the research study?
You will be one of about **90** people who will be participating in this study.

Genetic Testing
This study will not involve genetic research or genetic testing.

Specimen Banking (Future Use and Storage)
We will destroy the specimens and information about you when the study is complete. Information about you will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Information Banking (Future Use and Storage)
Information about you will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Will I be paid for being in this research study?
You will receive a total of RWF 24,000 for 3 study visits. You will receive RWF 8,000 in cash at the end of each visit. If you choose to withdraw from the study before all visits are completed, you will be paid only for the visits you completed.

Will it cost me anything to participate in this study?
Taking part in this study will not involve added costs to you. All care will be given free of charge as per Government of Rwanda policies.

Confidentiality
The researchers and study staff follow US federal and state laws as well as Government of Rwanda laws to protect your privacy. This part of the consent form tells you what information about you may be used and shared in the research described in this form. You do not have to sign this form but, if you do not, you may not participate in the research.

The health information that we may use or disclose for the research described in this form includes information from your entire medical record, such as your name, phone number, email, medical diagnoses, dates, test results, social security number, medical record numbers, etc.

Your information and research records will be kept confidential. Your study information will be kept as long as they are useful for the research described in this form.

The only people who can see your research records are:

- Researchers and other individuals who work with the researchers
- Organizations and institutions involved in this research, including those that fund the research, if applicable
- Groups that review research such as central reviewers, Institutional Review Boards, the Office for Human Research Protections, the US Food and Drug Administration, data coordinating centers, and domestic and foreign agencies that regulate research.

The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the study is being done correctly. The information covered under this form may no longer be protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who receive your health information may share your information with others without your additional permission. All of these groups have been asked to keep your information confidential.

Medical information collected during the research, such as test results, may be entered into your medical record and will be available to clinicians and other staff who provide care to you.

To maintain the integrity of this research study, you generally will not have access to your research-related personal health information. If it is necessary for your care, your research-related health information will be provided to you or your physician.

Are there any times you would not keep my data confidential?
If you give us information that suggests that your child or any other child is being abused, we are required by law to report that information to the Government of Rwanda agencies in charge of child protection. Reporting this information may put you, your family, or others who are involved at risk of questioning and legal action by the authorities.

If you give us information that you are in danger of hurting yourself, hurting someone else, or being hurt by someone else, we might not be able to keep this information confidential, and might need to share this information with social work or mental health staff at the health center in order to help you.

Certificate of Confidentiality
As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study were requested or subpoenaed by government agencies or the courts, we would use the Certificate to attempt to legally refuse to provide that information. These requests are rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations to which the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Are there any risks to me?
As part of this study you may have fewer regularly scheduled visits to the health center, which may put you at risk of worse adherence to your medications or appointments, or make you feel like you have less support from the health center.

A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of privacy means having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your privacy – see the Confidentiality section above for details.

Questionnaire
You may feel uncomfortable answering questions about your health, including about HIV. You can choose not to answer questions that make you feel uncomfortable.

Blood Draw
Rarely, the vein where we inserted the needle will become sore or red. Sometimes, a temporary harmless “black and blue” may develop. Very rarely, fainting may occur.

New Findings
If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them.

Are there possible benefits to me?
You may or may not receive personal, direct benefit from taking part in this study. The possible benefits of taking part in this study include coming to the health center less frequently, which may reduce your burden of care.

What choices do I have other than participating in this study?
You can refuse to participate in the study. If you decide not to participate, the medical care providers at this facility will still give you all of the standard care and treatment that is appropriate for you.

Are there any consequences to me if I decide to stop participating in this study?
No. If you decide to take part, you are free to stop participating at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility. However, some of the information may have already been entered into the study and that will not be removed. The researchers may continue to use and share the information they have already collected.

To revoke (take back) your consent and authorization, you must contact the Principal Investigator in writing at the address on page 1 of this form. However, you may first call or speak to the Principal Investigator and he will stop collecting new information about you. If you take back your consent and authorization, you will not be allowed to continue to participate in this research study.

Can the study end my participation early?
In addition, your participation will end if the investigator or study sponsor stops the study earlier than expected.

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant (not applicable for participants under age 13)	Date	Time
Printed Name of Parent or Guardian (when applicable)	Signature of Parent or Guardian (when applicable)	Date	Time
Printed name of the person conducting the consent process	Signature	Date	Time

SPIRIT CHECKLIST

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	16,17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9,10,Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11, 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking)	11

		should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9,12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13,14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for a pilot, unblinded, randomized controlled study.

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Reducing time to differentiated service delivery for newly-diagnosed people living with HIV in Kigali, Rwanda: study protocol for a pilot, unblinded, randomized controlled study.

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ABSTRACT

Introduction: Current HIV guidelines recommend differentiated service delivery (DSD) models that allow for fewer health center visits for clinically stable people living with HIV (PLHIV). Newly-diagnosed PLHIV may require more intensive care early in their treatment course, yet frequent appointments can be burdensome to patients and health systems. Determining the optimal parameters for defining clinical stability and transitioning to less frequent appointments could decrease patient burden and health system costs. The objectives of this pilot study are to explore the feasibility and acceptability of: 1) reducing the time to DSD from 12 to 6 months after antiretroviral therapy (ART) initiation, and 2) reducing the number of suppressed viral loads required to enter DSD from two to one.

Methods and analyses: The present study is a pilot, unblinded trial taking place in three health facilities in Kigali, Rwanda. Current Rwandan guidelines require PLHIV to be on ART for ≥12 months with two consecutive suppressed viral loads in order to transition to less frequent appointments. We will randomize 90 participants to one of three arms: entry into DSD at six months after one suppressed viral load (N=30), entry into DSD at six months after two suppressed viral loads (N=30), or current standard of care (N=30). We will measure feasibility and acceptability of this intervention; clinical outcomes include viral suppression at 12 months (primary outcome) and appointment attendance (secondary outcome).

Ethics and dissemination: This clinical trial was approved by the institutional review board of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee. Findings will be disseminated through conferences and peer-reviewed publications as well as meetings with stakeholders.

Trial registration: Clinicaltrials.gov [NCT04567693]

Strengths and limitations of this study

- This pilot, randomized, controlled trial examining clinical outcomes of newly-diagnosed people living with HIV who transition to differentiated service delivery models after shorter intervals in care or fewer viral load measurements will provide important evidence to inform HIV program implementation in Rwanda as well as globally.
- A three-armed study will be able to simultaneously explore the impact of: 1) reducing the time to differentiated service delivery from 12 to 6 months after antiretroviral therapy initiation, and 2) reducing the number of suppressed viral load measurements required to enter differentiated service delivery from two to one.
- Consideration of experienced and anticipated stigma as well as patient expenditures will provide additional information on the feasibility and acceptability of this model of care.
- The unblinded nature of this trial may lead to bias in subsequent clinical management and outcome ascertainment.
- The setting of the trial (urban health facilities in the capitol city of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa) may limit the generalizability of our findings.

INTRODUCTION

With the goal of ending the HIV pandemic, the UNAIDS "90-90-90" targets for 2020 are that 90% of all people living with HIV (PLHIV) know their HIV status, 90% of people with diagnosed HIV infection receive sustained antiretroviral therapy (ART), and 90% of all people receiving ART achieve viral suppression. [1] To this end, in 2015 the World Health Organization (WHO) recommended in its Treat All guidelines that all PLHIV initiate ART as quickly as possible after diagnosis.[2] Since implementation of its Treat All policy in 2016, Rwanda has nearly achieved UNAIDS 90-90-90 targets,[3] yet groups including men and younger PLHIV remain at higher risk of poorer outcomes. Reducing barriers to initiating and adhering to therapy is thus paramount to ensuring all PLHIV in Rwanda succeed in HIV therapy.

The 2016 WHO guidelines recommend differentiated service delivery (DSD) models as a strategy to manage diverse sets of patient needs.[2] Under these guidelines, PLHIV considered to be clinically stable – on ART for 1 year with 2 consecutive suppressed viral loads – can be seen less frequently for clinical assessments and dispensed ART for longer periods. Such approaches are feasible, acceptable, and achieve equivalent or improved retention in care and viral suppression.[4-8] To date, numerous countries in sub-Saharan Africa have adopted DSD models,[9] and some have modified eligibility for these programs in response to the Covid-19 pandemic as a means to promote social distancing.[10] While most DSD programs limit eligibility to patients who are clinically stable, heterogeneity exists with respect to definitions of stability. Some programs in sub-Saharan Africa use shorter intervals (i.e. 6 months after ART initiation) and/or only require a single suppressed viral load for categorization as stable.[9,11-13] To date, most studies of DSD models have been limited to clinically stable patients, and no studies have empirically compared clinical outcomes of newly-diagnosed PLHIV who transition to DSD models after shorter intervals in care or fewer viral load measurements compared to the current standard of care.

To optimize HIV program outcomes under Treat All, Rwanda simultaneously introduced differentiated service delivery (DSD) models to align services with the variable needs and preferences of different groups of PLHIV. [14] Stable PLHIV - adults on first- or second-line ART for ≥12 months with two consecutive suppressed viral loads - can collect ART every 3 months (rather than monthly) and attend clinical appointments every 3 or 6 months based on clinical criteria (**Table 1**). Individuals in the unstable category – including newly diagnosed

PLHIV (<12 months on ART), women who are pregnant or lactating, patients with concurrent mental health disorders, and PLHIV who are not virally suppressed – must visit the clinic monthly for ART collection and adherence assessment.

Our earlier research in Rwanda identified frequent appointments as burdensome to newly-diagnosed PLHIV because of structural issues such as transportation cost and long wait times, as well as stigma experienced while traveling to and while at the health center.[15] Modifying the definition of clinically stable adults living with HIV to decrease the time on ART and reduce the number of viral load measurements could potentially reduce the burden faced by patients and health systems. However, implementing DSD earlier in patients' treatment may not provide them with the support needed to become stable in care and achieve viral suppression.

We are therefore conducting a pilot, unblinded, three-arm randomized controlled trial to explore the impact of two less intensive DSD models: 1) reducing the time to DSD from 12 to 6 months after ART initiation, and 2) reducing the number of suppressed viral load measurements required to enter DSD from two to one. Our objectives are to understand whether these less-intensive DSD models are acceptable to participants and stakeholders, determine whether their implementation is feasible in the context of current Rwandan HIV guidelines, and obtain parameter estimates to guide future efficacy testing. This study will contribute relevant information and actionable information to inform DSD care delivery in Rwanda and help plan for a future, fully-powered study to test these models.

TABLE 1. Current differentiated care delivery model in Rwanda

	Standard of care	Differentiated Service Delivery	
	Unstable	**Stable A**	**Stable B**
Patient	• Patients on ART for <12 months • Severe mental health disorder • Pregnant or lactating • On ART but not virally suppressed • Patients on 3rd line ART • Children <2 years old	• Adults on 1st and 2nd line ART with 2 consecutive suppressed viral loads	• Children ≥2 years • Adolescents • Key populations • Co-infected with TB or hepatitis
Provider	Clinical nurse		
Service location	Health center		
Frequency of clinical visits	Every 3 months	Every 6 months	Every 3 months
Frequency of ART pick-up	Monthly	Every 3 months	Every 3 months

ART: antiretroviral therapy; TB: tuberculosis

METHODS AND ANALYSIS

Trial design

This three-arm, unblinded, parallel group randomized controlled trial will examine the feasibility and acceptability of reducing the time to DSD from 12 to 6 months as well as reducing from two to one the number of suppressed viral loads required to enter DSD, compared to usual care. The primary (viral suppression at 12 months after ART initiation) and secondary (appointment attendance over 12 months after ART initiation) efficacy outcomes will be compared using an exploratory, non-inferiority analysis.

Study setting

Rwanda, a landlocked nation with a population of nearly 13 million, became one of the first sub-Saharan African countries to implement Treat All nationally in 2016. The Rwandan HIV program has been successful, with recent estimates of >95% of PLHIV on ART and viral suppression >90%.[3,16] Rwanda has a pyramidal health system, with 8 national referral hospitals, 36 district hospitals, and nearly 500 public health centers. Primary health care is predominantly delivered at health centers, which provide health promotion, preventive and treatment services in medicine, surgery, obstetrics and pediatrics, and are largely staffed by nurses. HIV care in Rwanda is decentralized and provided at nearly all health centers, and includes diagnostic testing, chronic disease management, and ART. Current guidelines in Rwanda specify that all newly-diagnosed patients should be on one of two ART regimens: tenofovir disoproxil fumarate, lamivudine and dolutegravir, or abacavir, lamivudine and dolutegravir.[17]

This study will be carried out in three health facilities located in Rwanda's capital city, Kigali: Gikondo Health Center, Kicukiro Health Center, and Remera Health Center. Together, these health facilities provide primary HIV care to approximately 6,000 PLHIV, including approximately 300 newly-diagnosed patients who enroll in care annually.

Eligibility

Inclusion criteria for this study are: 1) ≥15 years of age; 2) newly-diagnosed with HIV within prior 6 months; 3) enrolled in HIV care at a participating study health facility within prior 30 days; 4) initiated ART. Exclusion criteria are: 1) planning on moving away from Kigali area

during 12-month duration of study; 2) pregnant or lactating at time of study enrollment; 3) co-infected with active tuberculosis at time of study enrollment; 4) concurrent known severe mental health or substance use disorder; 5) unable to provide informed consent.

Interventions

Participants will be randomized within 1 month of ART initiation to one of three arms in a 1:1:1 ratio, as follows. *Arm 1: Entry into the DSD model at six months after ART initiation with one suppressed viral load*. In this arm, participants will have their viral loads measured at 5 months after ART initiation. If the viral load is suppressed, they will advance to a spaced out appointment schedule of clinical appointments every six months and ART pick up every three months. *Arm 2: Entry into the DSD model at six months after ART initiation with two suppressed viral loads*. In this arm, participants will have viral loads measured at 3 and 5 months after ART initiation. If both are suppressed, they will advance to a spaced-out appointment schedule of clinical appointments every six months and ART pick up every three months. Because patients are expected to be on a dolutegravir-based regimen, we anticipate that those adherent to ART will have achieved viral suppression within 3 months of ART initiation. *Arm 3: Usual care*. In this arm, participants will have their viral loads measured at 5 months, but will continue on an appointment schedule of clinical appointments every three months and ART pick up monthly.

For participants in the intervention arms, the decision to advance patients to a DSD schedule is primarily contingent on their viral load measurements at three and/or five months. However, health care providers at the health facilities may determine that patients are not eligible for a spaced-out appointment schedule based on overall clinical assessment and override the study assignment. For example, individuals randomized to one of the intervention arms, but who subsequently become ineligible for a DSD schedule because of pregnancy will not be permitted to continue in the DSD schedule and will cross to the usual care arm. Participants in the usual care arm will not be eligible for advancement to a DSD schedule until the study ends, however, those in the intervention arms may choose to attend appointments more frequently if agreed to by their clinician. All instances in which health center staff determine that participants cannot advance to or continue in a spaced-out appointment schedule, including the reason for the change and whether it was initiated by the clinician or patient, will be recorded.

Before the study begins enrollment, staff at participating health facilities will receive training on the study protocol including eligibility criteria, study design and appointment schedules for the three arms. Throughout the study, the research team will regularly communicate with health facility staff to ensure that eligible study participants in the intervention arms advance to a spaced-out appointment schedule. The study team will review participant medical files to assess fidelity to the appointment schedule. While appointment schedules will be dictated by the study protocol, all other clinical treatments will be at the discretion of health facility clinicians. Following the trial, participants will continue in regular HIV care at their health facility; those in the usual care arm who were virally suppressed on preceding measurements will be eligible for advancement to a DSD schedule at this time.

Outcomes

To explore the impact of less frequent appointments and virologic monitoring on patient outcomes, we will measure viral suppression (primary efficacy outcome) and appointment attendance (secondary efficacy outcome). Viral suppression will be measured as the proportion of participants in each arm who achieve viral suppression (viral load <200 copies/ml, based on current Rwandan guidelines) at 12 months after ART initiation. Appointment attendance will primarily be measured as the proportion of participants who attend all scheduled clinical and pharmacy visits over the first 12 months after ART initiation (11 in arms 1 and 2; 16 in arm 3), by reviewing participant medical records; we will also measure this outcome as the overall proportion of scheduled visits attended. Patients at study health centers who do not attend a scheduled appointment are called the next day to reschedule. If unsuccessful, appointments are considered missed; however, outreach efforts continue to be made.

Feasibility of an early spaced-out appointment schedule and less frequent virologic monitoring will also be examined using process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measures. We will also conduct structured interviews with health facility staff at the end of the study to determine feasibility of implementing this intervention at a larger scale.

Acceptability of an early spaced-out appointment schedule and less frequent virologic monitoring will be measured through: 1) surveys of satisfaction with health care [18,19]; 2) structured qualitative interviews with patients and health facility staff in all arms to understand

attitudes towards and satisfaction with various appointment schedules; 3) review of instances in which health center clinicians override the experimental assignment; and 4) review of adverse event logs.

We will also measure within-group change over time and differences between groups for the following tertiary outcomes:

- ART adherence will be collected using 7- and 30-day self-reported ART adherence measures at study entry, 6- and 12-months after ART initiation.
- Participant quality of life will be measured by the EuroQOL-5 Dimension-5 Levels (EQ-5D-5L),[20] which measures self-rated problems in 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as self-rated health. We will collect and report changes in quality of life at study entry, 6- and 12-months after ART initiation.
- Enacted, internalized, and anticipated stigma will be measured using a modified version of the HIV stigma scale [19] as well as the HIV/AIDS Stigma Instrument-PLWA (HASI-P) Scale.[21] We will measure stigma at study entry, 6- and 12-months after ART initiation.
- Participant health-related expenditures will be measured at study entry, 6- and 12-months after ART initiation.

STUDY PROCEDURES

Recruitment

Active recruitment will occur via health facility nurses who will inform potentially eligible patients about the study during their routine appointments. Each week a designated health facility staff member will provide the research assistant with a list of patients who indicated interest in participating and who meet eligibility criteria (i.e. newly-diagnosed, not pregnant or lactating, without severe mental health conditions). Passive recruitment will occur through research assistants who will also make general announcements about the study during morning health education sessions at health facilities, and be available to answer questions and collect interested patient's contact information. Interested patients will be screened by study staff for eligibility, and if eligible will be offered enrollment in the study.

Study timeline

The study enrollment visit will occur within 30 days of the patient's enrollment in HIV care at the health center. All participants will have additional research visits six and twelve months after enrolling in HIV care. Research visits will entail participant interviews and medical record review. Participants will also visit the health facility for viral load measurements at three and five months after ART initiation, depending on the study arm. Participants will be reimbursed for all research and viral load visits. **Table 2** describes the schedule of clinical and research visits. At the conclusion of the study enrollment visit, the research assistant will give the participant a reminder card with the date of the next research visit. Study staff will call the participant one week and one day before the scheduled research visits to remind them of the appointment date and time. Participants who do not appear for scheduled research visits will be called and visits rescheduled within 14 days. Research staff will not provide reminders for clinical or pharmacy visits.

TABLE 2. Schedule of health center and research visits.

	Health center and research visits after ART initiation (months)											
TIMEPOINT (Month)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
INTERVENTION: appointment and viral load schedule												
Arm 1 (Early DSD after one suppressed viral load)												
Clinical appointments			●			●						●
ART pick-up	●	●	●	●	●	●			●			●
Viral load measurement					●							●
Arm 2 (Early DSD after two suppressed viral loads)												
Clinical appointments			●			●						●
ART pick-up	●	●	●	●	●	●			●			●
Viral load measurement			●		●							●
Arm 3 (Usual care)												
Clinical appointments			●			●			●			●
ART pick-up	●	●	●	●	●	●	●	●	●	●	●	●
Viral load measurement					●							●
RESEARCH VISITS (All arms)	●					●						●

ART: antiretroviral therapy; DSD: differentiated care delivery

Informed consent

Newly-diagnosed PLHIV who have enrolled in care within 30 days and meet eligibility criteria will be referred to the study team. At study entry, written, informed consent to participate

will be obtained from all participants (Supplemental File 1, Model consent form). Participants aged 15-18 will provide assent with informed consent obtained from their parent or legal guardian. Research staff will read the informed consent document to participants in its entirety; participants unable to sign their name will be permitted to sign with an "X." No additional consent provisions are required for collection and use of participant medical record data and biological specimens in this study.

Randomization

At study entry, participants will be randomized to one of three study arms. To ensure equal distribution of key factors among randomization arms, we will stratify randomization by age group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure comparison groups of approximately equal size. Randomization will be computer generated, occur in blocks of 6 with 1:1:1 allocation across study arms.

To ensure concealment of allocation, a centrally-located data manager will generate the allocation sequence and store the sequence in a password-protected file. Since the intervention is not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The allocation sequence will be generated using the Proc Plan function in SAS (9.4). Upon enrollment in the study, research staff will use the randomization function in REDCap (Research Electronic Data Capture, v10.0.16, 2020, Vanderbilt University) to assign participants to study arms. Because this study is examining the effect of different appointment schedules, it is not feasible to blind participants or study personnel, and thus allocation will not be concealed from staff or participants.

Data collection

Data will be collected through participant interviews, laboratory tests and medical record review. Research staff will be trained in systematic data collection by interview. Interviews will be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime protocols will be implemented in the event of internet outage. Medical records will be reviewed at the end of every study visit, with data entered directly into REDCap. Venous blood specimens for clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several subsequent visits during the study. Results will be provided to clinical staff at health facilities,

who will input them into the medical record and report them to participants, consistent with routine clinical practices. Viral load measurements will be performed using the Abbott Allinity m instrument, with a lower limit of detection of 20 copies/ml. No genetic or molecular analyses will be performed; specimens will not be stored for future use.

Analytic approach

We expect to enroll 90 participants into this study. This pilot study is designed to test feasibility and acceptability and is thus not powered for hypothesis testing. Sample size was determined based on available resources for conducting the study. The primary analyses will be by intention to treat.

Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the data, examining frequencies, means, medians and ranges to identify any systematic or logical errors. As this is a pilot study, analyses will be descriptive in nature. Validated instruments will be coded according to respective scoring instructions. Feasibility will be examined using descriptive analyses to describe process measures including proportion eligible, consented, randomized, the proportion of participants attending appointments in each arm, and cost measurements. We will also conduct thematic analysis of qualitative, structured interviews to determine intervention acceptability of less intensive DSD models as well as feasibility of implementing this intervention at a larger scale.

For the outcomes of viral suppression and appointment adherence, the primary analysis will be intention to treat including all randomized participants, with those who are missing outcome data considered treatment failures. We will first compare study arms with respect to the proportions of patients achieving viral suppression and attending all clinical and pharmacy visits using chi-square tests. We will then use logistic regression to estimate odds ratios and associated 95% confidence intervals for the effect of each intervention arm compared to the control, adjusting for key baseline covariates that are imbalanced between groups. Because of the small number of participants we anticipate enrolling in this pilot study, we will not be sufficiently powered to detect statistically significant differences in outcomes. However, the findings obtained from this study will provide key results on intervention feasibility and guide a future, larger study to test intervention efficacy.

Due to the pilot nature of this study, relatively short duration, and small planned enrollment size, we do not plan on conducting interim analyses. In secondary analyses, we will examine outcomes of viral suppression and appointment attendance using a per-protocol approach. We will also compare statistical results using a dataset with imputed values and the dataset that drops missing values, guiding our interpretation of the impact of missing data on findings, as well as our interpretation of overall results. Moreover, because outcome data may be missing for different reasons, we will document reasons for missingness to the degree possible to inform these additional analyses. For example, while the number of deaths is anticipated to be small, we will conduct analyses both including and excluding participants who died to understand the potential impact of death on results. Additional sub-analyses will examine outcomes separately among subgroups of interest (i.e. men, young patients, early defaulters) though these may be limited by the small size of some subgroups.

Data management

In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g. range checks, logical dates) and store interview, medical record and laboratory data. No identifying information will be collected in REDCap. Only research investigators and staff will have access to study databases. Data quality will be promoted through training research staff to uniformly collect and enter data and by periodic data quality monitoring.

Confidentiality

The following measures will be utilized to protect participant confidentiality: All paper study records (i.e. informed consent documents) will be kept in locked file cabinets with access limited to study staff. In accordance with Rwandan research regulations, all personally identifying information, including participant names and contact information, will be collected using a locally-stored, password-protected, encrypted database. REDCap data will not include any name-based or identifying information. Study databases will be maintained on encrypted, password-protected computers and servers to which only study staff will have access. To prevent linking of sensitive material to participants' personal identifiers, we will utilize separate "name-based" and

"ID-based" systems. For any paper forms, all documents that have patient identifiers (e.g. consent forms, locator forms) will be filed together. Any files that do not include identifying information or signatures will only use participants' unique, study-specific IDs (rather than names) and will be filed separately from name-based documents. There will only be one electronic document that links participants' names to their study IDs, stored on a local, password-protected, encrypted server. Publication or presentation of study results will not identify subjects.

Study oversight

This is a pilot study of approximately 90 participants being conducted to test feasibility and acceptability of a modified appointment schedule. This is a low risk study that involves pilot testing an intervention that will enroll a relatively small number of participants, and it is unlikely that study participants will experience adverse reactions related to study participation. Therefore there will not be a Data Safety and Monitoring Board. The study team, consisting of the PI, co-investigators, and research staff, meet weekly to review study progress, including review of adverse events. If adverse events occur, the PI will act to minimize their impact and ensure the adverse event is reported to the responsible authorities in a timely manner as required. There is no coordinating center or steering committee. This pilot trial will not be audited.

Adverse event reporting and harms

The PI, together with the study team, will be responsible for regularly monitoring data and safety, specifically assessing for adverse events and breach of confidentiality. If adverse events occur, the study team will: 1) identify the concern, 2) activate the appropriate response to minimize the adverse event, and 3) ensure the adverse event is reported to the responsible authority in a timely manner. If patients have a medical or psychiatric decompensation during the study, research staff will inform their direct supervisor, who will assess the patient in-person, and will notify the PI or co-investigators immediately. Based on clinical judgment, study participants will be referred to psychiatric or medical consultation in the health facility or referred for emergency care. The study database will be secured with encryption and password protection, and the study team will monitor the database for potential breaches of confidentiality.

All adverse events will be compiled monthly. Unanticipated, non-serious adverse events will be documented and reported by the PI to the Albert Einstein College of Medicine IRB and the Rwanda National Ethics Committee within 30 days. Serious adverse events will be reported by the PI to the Albert Einstein College of Medicine IRB and Rwanda National Ethics Committee within 48 hours by phone, email, or fax.

Discussion

This trial will pilot test reducing the time to DSD from 12 to 6 months as well as reducing the number of suppressed viral loads required to enter DSD from two to one, compared to usual care. If found feasible and acceptable, this approach could reduce inconvenience and stigma for newly-diagnosed PLHIV as well as lower the medical resources required for treatment.

This study may face potential limitations. Participants in the intervention arm with two viral load measurements effectively have twice as many opportunities to not be virally suppressed, with viral suppression less likely at 3 compared to 5 months, and therefore may be less likely to advance to DSD. Similarly, participants will advance to DSD at the discretion of treating clinicians. This may bias the study findings if participants in the intervention arms effectively follow the standard of care, and may result in less power to detect differences between the study arms in the intention to treat analysis. Nonetheless, the study will provide important feasibility and acceptability data on the optimal number of viral load measurements needed to determine clinical stability. Because inclusion criteria specify HIV diagnosis within the preceding 6 months, it is possible that participants will have been in care elsewhere and defaulted prior to enrolling in study health centers, and thus not ART-naïve. While it may not be possible to know if patients are truly newly-diagnosed, we expect that any early defaulters would be equally distributed between arms given the randomized nature of this study, and thus would not impact analysis of outcomes. Blinding will not be feasible for this study, which may bias the study findings. ART adherence will be measured by self-report, which may imperfectly reflect true medication adherence. Finally, we will be enrolling patients who receive care at health facilities located in or near the capital of a country with a highly functional HIV care service delivery system and with a lower HIV prevalence than in much of southern Africa. This may limit the generalizability of our findings.

DSD models, including less frequent appointment schedules, are increasingly being adopted across HIV care settings globally, and are acceptable to patients and cost-effective.[4-8, 22-23] A key question in implementing DSD models is determining at what point patients receiving HIV care can be considered clinically stable. By examining the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally.

Patient and public involvement

The design of this study was informed by findings of formative, qualitative research conducted with patients at study health centers,[15] clinical experiences of several of the authors, along with input from public health and clinical leaders in Rwanda. The research questions and design were reviewed by investigators with expertise in HIV health services delivery and infectious diseases, along with input from an advisory committee consisting of leadership from study health centers as well as the Rwanda Biomedical Center, the nation's central health implementation agency.

ETHICS AND DISSEMINATION

This clinical trial was approved by the institutional review board (IRB) of Albert Einstein College of Medicine and by the Rwanda National Ethics Committee and is registered on www.clinicaltrials.gov [NCT04567693].

By examining the effect of reduced time to DSD as well as fewer viral load measurements prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in Rwanda as well as globally. We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to patients, providers and key institutional stakeholders. Study findings will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) standards.

TRIAL STATUS

The current protocol is version 1.4, dated 28 September 2020. Any important protocol amendments will be communicated immediately to the responsible ethical committees and will be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is expected to continue until August 2021, with follow-up continuing until August 2022.

AUTHOR'S CONTRIBUTIONS

JR is the Principal Investigator; he conceived the study, led the proposal and protocol development. SH, CI, FU, AM, BM, GM, and KA contributed to study design and to development of the proposal. ER, DSH, PM, and MY provided additional input to study design. CZ provided statistical support. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests or conflicts of interest to disclose.

DATA AVAILABILITY

The final trial dataset will not be released publicly based on policies of the Rwandan Ministry of Health. In August 2024 (two years after the conclusion of data collection), the dataset can be shared on upon written request to, and after review and approval by, Dr. Gad Murenzi (gadcollins@gmail.com).

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KEY INFORMATION FOR *REDUCING TIME TO SPACED-OUT APPOINTMENTS FOR NEWLY-DIAGNOSED PEOPLE LIVING WITH HIV*

We are asking you to choose whether or not to volunteer for a research study about the best way to schedule appointments for people who are newly diagnosed with HIV. This page is designed to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn whether an appointment schedule with fewer appointments will make it easier for patients living with HIV to get their care. We will compare different appointment schedules to understand the costs and benefits of each one. Your participation in this research will last about 1 year.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You will not receive any direct benefit from participating in this study. However, some participants appreciate knowing they have contributed to research that may benefit others in the future.

For a complete description of benefits, refer to the Consent Document below.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may not want to participate in this study if you are worried about keeping your information absolutely private. In addition, sometimes answering questions about your health can be stressful.

For a complete description of alternate treatment/procedures, refer to the Consent Document below.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights or access to care you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The persons in charge of the study are Dr. Gad Murenzi (Rwanda) and Dr. Jonathan Ross (US) If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is:.

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

If you are a parent or legal guardian of a child who may take part in this study, permission from you and the assent (agreement) of your child may be required. When the word "you(r)" / "my" / "me" / "I" appears in this consent form, we mean the participant (you or your child); "we" means the research study doctors and research staff.

Introduction

You are being asked to participate in a research study called ***REDUCING TIME TO SPACED-OUT APPOINTMENTS FOR NEWLY-DIAGNOSED PEOPLE LIVING WITH HIV*.** Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no", your decision will not affect any of your rights or benefits or your access to care.

Why is this study being done?

The goal of this study is to understand whether there are benefits or harms from having less frequent appointments for HIV care starting at 6 months after diagnosis. Right now, people living with HIV in Rwanda must come to appointments often for the first 12 months after diagnosis, which can be difficult. We want to test whether having patients come less frequently will have an effect on patients' adherence to medication or appointments. We think that coming less frequently will not lead to worse adherence.

Why am I being asked to participate?

You are being asked to participate in this study because you are a person living with HIV, are at least 15 years old and are receiving health care from one of the health centers participating in the study. You are being asked to take part because you heard about the study from someone who works at the health center or from the research staff. In total, we expect approximately 90 people from 3 health facilities to take part in this study.

What will happen if I participate in the study?

If you choose to participate, you will be randomized to one of three appointment schedules. Randomization is like a coin flip. We do not control which schedule you will be assigned. The entire study will last for 1 year. In all schedules, you will continue to come to the health center until 6 months have passed since you first enrolled in care.

- In the first schedule, you will have a viral load checked two times between now and the 6-month point. If both viral loads are suppressed, then you will be scheduled to see the nurse every 6 months and come to the pharmacy for medication pick-up every 3 months.
- In the second schedule, you will have a viral load checked once between now and the 6-month point. If the viral load is suppressed, then you will be scheduled to see the nurse every 6 months and come to the pharmacy for medication pick-up every 3 months.
- In the third schedule, you will continue to come to the health center every 3 months to see the nurse and every month to the pharmacy for the entire study period.

As part of this study we will measure a few blood tests at the first and last research visits. These tests are the same tests that you would have done at the health center. To obtain the blood sample, we will wipe the skin on your arm with alcohol to clean it. Then, we will insert a small needle into a vein. Three tubes of blood will be drawn, about 20ml.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

As part of this study we will review your medical records and put the information we collect in our research records.

How many people will take part in the research study?
You will be one of about **90** people who will be participating in this study.

Genetic Testing
This study will not involve genetic research or genetic testing.

Specimen Banking (Future Use and Storage)
We will destroy the specimens and information about you when the study is complete. Information about you will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Information Banking (Future Use and Storage)
Information about you will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

Will I be paid for being in this research study?
You will receive a total of RWF 24,000 for 3 study visits. You will receive RWF 8,000 in cash at the end of each visit. If you choose to withdraw from the study before all visits are completed, you will be paid only for the visits you completed.

Will it cost me anything to participate in this study?
Taking part in this study will not involve added costs to you. All care will be given free of charge as per Government of Rwanda policies.

Confidentiality
The researchers and study staff follow US federal and state laws as well as Government of Rwanda laws to protect your privacy. This part of the consent form tells you what information about you may be used and shared in the research described in this form. You do not have to sign this form but, if you do not, you may not participate in the research.

The health information that we may use or disclose for the research described in this form includes information from your entire medical record, such as your name, phone number, email, medical diagnoses, dates, test results, social security number, medical record numbers, etc.

Your information and research records will be kept confidential. Your study information will be kept as long as they are useful for the research described in this form.

The only people who can see your research records are:

- Researchers and other individuals who work with the researchers
- Organizations and institutions involved in this research, including those that fund the research, if applicable
- Groups that review research such as central reviewers, Institutional Review Boards, the Office for Human Research Protections, the US Food and Drug Administration, data coordinating centers, and domestic and foreign agencies that regulate research.

The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the study is being done correctly. The information covered under this form may no longer be protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who receive your health information may share your information with others without your additional permission. All of these groups have been asked to keep your information confidential.

Medical information collected during the research, such as test results, may be entered into your medical record and will be available to clinicians and other staff who provide care to you.

To maintain the integrity of this research study, you generally will not have access to your research-related personal health information. If it is necessary for your care, your research-related health information will be provided to you or your physician.

Are there any times you would not keep my data confidential?
If you give us information that suggests that your child or any other child is being abused, we are required by law to report that information to the Government of Rwanda agencies in charge of child protection. Reporting this information may put you, your family, or others who are involved at risk of questioning and legal action by the authorities.

If you give us information that you are in danger of hurting yourself, hurting someone else, or being hurt by someone else, we might not be able to keep this information confidential, and might need to share this information with social work or mental health staff at the health center in order to help you.

Certificate of Confidentiality
As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study were requested or subpoenaed by government agencies or the courts, we would use the Certificate to attempt to legally refuse to provide that information. These requests are rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations to which the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Are there any risks to me?
As part of this study you may have fewer regularly scheduled visits to the health center, which may put you at risk of worse adherence to your medications or appointments, or make you feel like you have less support from the health center.

A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of privacy means having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your privacy – see the Confidentiality section above for details.

Questionnaire
You may feel uncomfortable answering questions about your health, including about HIV. You can choose not to answer questions that make you feel uncomfortable.

Blood Draw
Rarely, the vein where we inserted the needle will become sore or red. Sometimes, a temporary harmless “black and blue” may develop. Very rarely, fainting may occur.

New Findings
If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them.

Are there possible benefits to me?
You may or may not receive personal, direct benefit from taking part in this study. The possible benefits of taking part in this study include coming to the health center less frequently, which may reduce your burden of care.

What choices do I have other than participating in this study?
You can refuse to participate in the study. If you decide not to participate, the medical care providers at this facility will still give you all of the standard care and treatment that is appropriate for you.

Are there any consequences to me if I decide to stop participating in this study?
No. If you decide to take part, you are free to stop participating at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility. However, some of the information may have already been entered into the study and that will not be removed. The researchers may continue to use and share the information they have already collected.

To revoke (take back) your consent and authorization, you must contact the Principal Investigator in writing at the address on page 1 of this form. However, you may first call or speak to the Principal Investigator and he will stop collecting new information about you. If you take back your consent and authorization, you will not be allowed to continue to participate in this research study.

Can the study end my participation early?
In addition, your participation will end if the investigator or study sponsor stops the study earlier than expected.

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant (not applicable for participants under age 13)	Date	Time
Printed Name of Parent or Guardian (when applicable)	Signature of Parent or Guardian (when applicable)	Date	Time
Printed name of the person conducting the consent process	Signature	Date	Time

SPIRIT CHECKLIST

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	16,17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9,10,Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11, 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking)	11

		should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9,12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13,14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.