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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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3 **Reducing time to differentiated service delivery for newly-diagnosed people living with**
4 **HIV in Kigali, Rwanda: study protocol for an exploratory, unblinded randomized control**
5 **study.**
6

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1 ABSTRACT

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

12
13 **Methods and analyses:** The present study is an exploratory, unblinded trial taking place in three
14 health facilities in Kigali, Rwanda. Current Rwandan guidelines require PLWH to be on ART for
15 ≥ 12 months with two consecutive suppressed viral loads in order to transition to less frequent
16 appointments. We will randomize 90 participants to one of three arms: entry into DSD at six
17 months after one suppressed viral load (N=30), entry into DSD at six months after two
18 suppressed viral loads (N=30), or current standard of care (N=30). We will measure feasibility,
19 acceptability and preliminary efficacy of this intervention; clinical outcomes include viral
20 suppression at 12 months (primary outcome) and appointment attendance (secondary outcome).

21
22 **Ethics and dissemination:** This clinical trial was approved by the institutional review board of
23 Albert Einstein College of Medicine and by the Rwanda National Ethics Committee. Findings
24 will be disseminated through conferences and peer-reviewed publications as well as meetings
25 with stakeholders.

26
27 **Trial registration:** Clinicaltrials.gov [NCT04567693]
28
29

30 **Strengths and limitations of this study**

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

46 INTRODUCTION

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

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

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

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

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

90 **METHODS AND ANALYSIS**

91 **Trial design**

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

99 **Study setting**

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

1
2
3 107 nurses. HIV care in Rwanda is decentralized and provided at nearly all health centers, and
4
5 108 includes diagnostic testing, chronic disease management, and ART.

6
7 109 This study will be carried out in three health facilities located in Rwanda's capital city,
8
9 110 Kigali: Gikondo Health Center, Kicukiro Health Center, and Rwanda Military Hospital.
10
11 111 Together, these health facilities provide primary HIV care to approximately 6,000 PLWH,
12
13 112 including approximately 300 newly-diagnosed patients who enroll in care annually.
14
15 113

15 114 **Eligibility**

16
17 115 Inclusion criteria for this study are: 1) ≥ 15 years of age; 2) newly-diagnosed with HIV within
18
19 116 prior 6 months; 3) enrolled in HIV care at a participating study health facility within prior 30
20
21 117 days; 4) initiated ART. Exclusion criteria are: 1) planning on moving away from Kigali area
22
23 118 during 12-month duration of study; 2) pregnant at time of study enrollment; 3) co-infected with
24
25 119 active tuberculosis at time of study enrollment; 4) concurrent known severe mental health or
26
27 120 substance use disorder; 5) unable to provide informed consent.
28
29 121

29 122 *Interventions*

30
31 123 Participants will be randomized to one of three arms in a 1:1:1 ratio, as follows. *Arm 1: Entry*
32
33 124 *into the DSD model at six months after enrollment in HIV care with one suppressed viral load.* In
34
35 125 this arm, participants will have their viral loads measured at 5 months after enrollment in HIV
36
37 126 care. If the viral load is suppressed, they will advance to a spaced out appointment schedule of
38
39 127 clinical appointments every six months and ART pick up every three months. *Arm 2: Entry into*
40
41 128 *the DSD model at six months after enrollment in HIV care with two suppressed viral loads.* In
42
43 129 this arm, participants will have viral loads measured at 3 and 5 months after enrollment in HIV
44
45 130 care. If both are suppressed, they will advance to a spaced-out appointment schedule of clinical
46
47 131 appointments every six months and ART pick up every three months. *Arm 3: Usual care.* In this
48
49 132 arm, participants will have their viral loads measured at 5 months, but will continue on an
50
51 133 appointment schedule of clinical appointments every three months and ART pick up monthly.

52
53 134 For participants in the intervention arms, the decision to advance patients to a DSD schedule
54
55 135 is primarily contingent on their viral load measurements at three and/or five months. Health care
56
57 136 providers at the health facilities may determine that patients are not eligible for a spaced-out
58
59 137 appointment schedule based on clinical assessment.
60

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3 138 Before the study begins enrollment, staff at participating health facilities will receive training
4
5 139 on the study protocol including eligibility criteria, study design and appointment schedules for
6
7 140 the three arms. Throughout the study, the research team will regularly communicate with health
8
9 141 facility staff to ensure that eligible study participants in the intervention arms advance to a
10
11 142 spaced-out appointment schedule. The study team will review participant medical files to assess
12
13 143 fidelity to the appointment schedule. While appointment schedules will be dictated by the study
14
15 144 protocol, all other clinical treatments will be at the discretion of health facility clinicians.
16
17 145 Following the trial, participants will continue in regular HIV care at their health facility.
18

19 147 **Outcomes**

20 148 To determine the preliminary efficacy of less frequent appointments and virologic monitoring
21
22 149 on patient outcomes, we will measure viral suppression (primary efficacy outcome) and
23
24 150 appointment attendance (secondary efficacy outcome). Viral suppression will be measured as the
25
26 151 proportion of participants in each arm who achieve viral suppression (viral load <200 copies/ml)
27
28 152 at 12 months after enrollment into HIV care. Appointment attendance will primarily be measured
29
30 153 as the proportion of participants who attend all clinical visits over the first 12 months after ART
31
32 154 initiation, by reviewing participant medical records; we will also measure this outcome as the
33
34 155 overall proportion of scheduled visits attended.

35 156 Feasibility of an early spaced-out appointment schedule and less frequent virologic
36
37 157 monitoring will be examined using process measures including proportion eligible, consented,
38
39 158 randomized, the proportion of participants attending appointments in each arm, and cost
40
41 159 measures. We will also conduct structured interviews with health facility staff at the end of the
42
43 160 study to determine feasibility of implementing this intervention at a larger scale.

44 161 Acceptability of an early spaced-out appointment schedule and less frequent virologic
45
46 162 monitoring will be measured through surveys of satisfaction with health care [10,11] as well as
47
48 163 structured qualitative interviews with patients and health facility staff in all arms to understand
49
50 164 attitudes towards and satisfaction with various appointment schedules, as well as a review of
51
52 165 adverse event logs.

53 166 We will also measure the following:

- 54 167 • Changes in ART adherence will be collected by participant self-report at study entry, 6-
55 168 and 12-months after ART initiation.

- 1
2
3 169 ● Changes in participant quality of life will be measured by the EuroQOL-5 Dimension-5
4 170 Levels (EQ-5D-5L),[12] which measures self-rated problems in 5 domains (mobility,
5 171 self-care, usual activities, pain/discomfort and anxiety/depression) as well as self-rated
6 172 health. We will collect and report changes in quality of life at study entry, 6- and 12-
7 173 months after ART initiation.
8
9 174 ● Changes in enacted, internalized, and anticipated stigma will be measured using a
10 175 modified version of the HIV stigma scale [10] as well as the HIV/AIDS Stigma
11 176 Instrument-PLWA (HASI-P) Scale.[13] We will measure stigma at study entry, 6- and
12 177 12-months after ART initiation.
13
14 178 ● Changes in participant health-related expenditures will be measured at study entry, 6- and
15 179 12-months after ART initiation.
16
17 180

181 STUDY PROCEDURES

182 Recruitment

183 Active recruitment will occur via health facility nurses who will inform potentially eligible
184 patients about the study during their routine appointments. Each week a designated health facility
185 staff member will provide the research assistant with a list of patients who indicated interest in
186 participating. Passive recruitment will occur through research assistants who will also make
187 general announcements about the study during morning health education sessions at health
188 facilities, and be available to answer questions and collect interested patient's contact
189 information. Interested patients will be screened for eligibility, and if eligible will be offered
190 enrollment in the study.
191

192 Study timeline

193 The study enrollment visit will occur within 30 days of the patient's enrollment in HIV care.
194 All participants will have additional research visits six and twelve months after enrolling in HIV
195 care. Research visits will entail participant interviews and medical record review. Participants
196 will also visit the health facility for viral load measurements at three and five months after
197 enrolling HIV care, depending on the study arm. **TABLE 1** describes the schedule of research
198 visits and data assessments.
199

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

TIMEPOINT (Month)	ART initiation	STUDY ENTRY	Allocation	STUDY PERIOD											
				Post-allocation											Close-out
				1	2	3	4	5	6	7	8	9	10	11	
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					•					•					•

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3 202 At the conclusion of the study enrollment visit, the research assistant will give the participant
4
5 203 a reminder card with the date of the next research visit. Study staff will call the participant one
6
7 204 week and one day before the scheduled research visits to remind them of the appointment date
8
9 205 and time. Participants who do not appear for scheduled research visits will be called and visits
10
11 206 rescheduled within 14 days. Research staff will not provide reminders for clinical or pharmacy
12
13 207 visits.
14

208

209 **Informed consent**

15
16
17 210 Newly-diagnosed PLWH who have enrolled in care within 30 days and meet eligibility
18
19 211 criteria will be referred to the study team. At study entry, written, informed consent to participate
20
21 212 will be obtained from all participants or their parent or legal guardian. No additional consent
22
23 213 provisions are required for collection and use of participant medical record data and biological
24
25 214 specimens in this study.
26

215

216 **Randomization**

27
28
29 217 At study entry, participants will be randomized to one of three study arms. To ensure equal
30
31 218 distribution of key factors among randomization arms, we will stratify randomization by age
32
33 219 group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure
34
35 220 comparison groups of approximately equal size. Randomization will be computer generated,
36
37 221 occur in blocks of 6 with 1:1:1 allocation across study arms.

38 222 To ensure concealment of allocation, a centrally-located data manager will generate the
39
40 223 allocation sequence and store the sequence in a password-protected file. Since the intervention is
41
42 224 not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The
43
44 225 allocation sequence will be generated using SAS (9.4). Upon enrollment in the study, research
45
46 226 staff will use the randomization function in REDCap (Research Electronic Data Capture,
47
48 227 v10.0.16, 2020, Vanderbilt University) to assign participants to study arms. Because this study is
49
50 228 testing the effect of different appointment schedules, it is not feasible to blind participants or
51
52 229 study personnel, and thus allocation will not be concealed from staff or participants.

230

231 **Data collection**

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3 232 Data will be collected through participant interviews, laboratory tests and medical record
4
5 233 review. Research staff will be trained in systematic data collection by interview. Interviews will
6
7 234 be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime
8
9 235 protocols will be implemented in the event of internet outage. Medical records will be reviewed
10
11 236 at the end of every study visit, with data entered directly into REDCap. Blood specimens for
12
13 237 clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several
14
15 238 subsequent visits during the study, and results reported to participants and to clinical staff at
16
17 239 health facilities. No genetic or molecular analyses will be performed; specimens will not be
18
19 240 stored for future use.

20

21 241 **Analytic approach**

22 242 We expect to enroll 90 participants into this study. This pilot study is designed to test
23
24 243 acceptability, feasibility and preliminary efficacy, and is thus not powered for hypothesis testing.
25
26 244 Sample size was determined based on available resources for conducting the study. The primary
27
28 245 analyses will be by intention to treat.

29 246 Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the
30
31 247 data, examining frequencies, means, medians and ranges to identify any systematic or logical
32
33 248 errors. As this is a pilot, exploratory study, analyses will be descriptive in nature. Validated
34
35 249 instruments will be coded according to respective scoring instructions. Feasibility will be
36
37 250 examined using descriptive analyses to describe process measures including proportion eligible,
38
39 251 consented, randomized, the proportion of participants attending appointments in each arm, and
40
41 252 cost measurements. We will also conduct thematic analysis of qualitative, structured interviews
42
43 253 to determine intervention acceptability of less intensive DSD models as well as feasibility of
44
45 254 implementing this intervention at a larger scale.

46 255 For the preliminary efficacy outcome of viral suppression, we will first compare proportions
47
48 256 of patients achieving viral suppression and attending all appointment/pharmacy visits using chi-
49
50 257 square tests. We will then use generalized estimating equations to estimate risk differences, risk
51
52 258 ratios and associated 95% confidence interval for the effect of each intervention arm compared to
53
54 259 the control. Intervention arms will be considered non-inferior to usual care if the lower margin of
55
56 260 the 95% confidence interval of the difference between risk ratios does not extend more than 10%
57
58 261 below the equivalence point, based on an expected 90% viral suppression rate in the control arm
59
60 262

1
2
3 263 (3). Because of the small number of participants we anticipate enrolling in this pilot study, we
4
5 264 may not be sufficiently powered to detect statistically significant differences in outcomes.
6
7 265 However, the findings and the effect size obtained from this study will provide key results on
8
9 266 intervention feasibility and guide a future, larger study to test intervention efficacy.

10 267 Due to the pilot nature of this study, relatively short duration, and small planned enrollment
11
12 268 size, we do not plan on conducting interim analyses or subgroup analyses. Data will be analyzed
13
14 269 using an intention-to-treat approach. We will not impute missing data.

15 270

17 271 **Data management**

18
19 272 In accordance with Rwandan research regulations, all personally identifying information,
20
21 273 including participant names and contact information, will be collected using a locally-stored,
22
23 274 password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g.
24
25 275 range checks, logical dates) and store interview, medical record and laboratory data. No
26
27 276 identifying information will be collected in REDCap. Only research investigators and staff will
28
29 277 have access to study databases. Data quality will be promoted through training research staff to
30
31 278 uniformly collect and enter data and by periodic data quality monitoring.

32 279

33 280 **Confidentiality**

34 281 The following measures will be utilized to protect participant confidentiality: All paper study
35
36 282 records (i.e. informed consent documents) will be kept in locked file cabinets with access limited
37
38 283 to study staff. In accordance with Rwandan research regulations, all personally identifying
39
40 284 information, including participant names and contact information, will be collected using a
41
42 285 locally-stored, password-protected, encrypted database. REDCap data will not include any name-
43
44 286 based or identifying information. Study databases will be maintained on encrypted, password-
45
46 287 protected computers and servers to which only study staff will have access. To prevent linking of
47
48 288 sensitive material to participants' personal identifiers, we will utilize separate "name-based" and
49
50 289 "ID-based" systems. For any paper forms, all documents that have patient identifiers (e.g.
51
52 290 consent forms, locator forms) will be filed together. Any files that do not include identifying
53
54 291 information or signatures will only use participants' unique IDs (rather than names) and will be
55
56 292 filed separately from name-based documents. There will only be one electronic document that

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

295

296 **Study oversight**

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

307

308 **Adverse event reporting and harms**

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

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

324 Discussion

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

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

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

350 Patient and public involvement

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

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2
3 355 infectious diseases, along with input from an advisory committee consisting of leadership from
4
5 356 study health centers as well as the Rwanda Biomedical Center, the nation's central health
6
7 357 implementation agency.

8 358

10 359 **ETHICS AND DISSEMINATION**

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12 360 This clinical trial was approved by the institutional review board (IRB) of Albert Einstein
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14 361 College of Medicine and by the Rwanda National Ethics Committee and is registered on
15
16 362 www.clinicaltrials.gov [NCT04567693].

17 363 By testing the effect of reduced time to DSD as well as fewer viral load measurements prior
18
19 364 to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial,
20
21 365 and provide practical data for HIV program implementation in Rwanda as well as globally.

22 366 We will disseminate study findings through presentations at scientific conferences, publications
23
24 367 in peer-reviewed journals, and presentations to patients, providers and key institutional
25
26 368 stakeholders. Study findings will be reported in accordance with the Consolidated Standards of
27
28 369 Reporting Trials (CONSORT) standards.

29 370

31 371 **TRIAL STATUS**

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33 372 The current protocol is version 1.4, dated 28 September 2020. Any important protocol
34
35 373 amendments will be communicated immediately to the responsible ethical committees and will
36
37 374 be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is
38
39 375 expected to continue until August 2021, with follow-up continuing until August 2022.

40 376

42 377 **AUTHOR'S CONTRIBUTIONS**

43
44 378 JR is the Principal Investigator; he conceived the study, led the proposal and protocol
45
46 379 development. SH, CI, FM, AM, BM, GM, and KA contributed to study design and to
47
48 380 development of the proposal. ER, DSH, PM, and MY provided additional input to study design.
49
50 381 CZ provided statistical support. All authors read and approved the final manuscript.

51 382

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16
17 394 +1.718.920.4321. The study sponsor and funder have no role in study design; collection,
18
19 395 management, analysis, and interpretation of data; writing of the report; and the decision to
20
21 396 submit the report for publication.

22 397

23 398 **COMPETING INTERESTS**

24 399 The authors declare that they have no competing interests or conflicts of interest to disclose.

25 400

26 401 **DATA AVAILABILITY**

27 402 The final trial dataset will not be released publicly based on policies of the Rwandan Ministry
28
29 403 of Health. In August 2023 (two years after the conclusion of data collection), the dataset can be
30
31 404 shared on upon written request to, and after review and approval by, Dr. Gad Murenzi
32
33 405 (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

1	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
2				
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4				
5	Methods: Participants, interventions, and outcomes			
6	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
7				
8				
9	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
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12	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
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15		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
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18		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,10
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21		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7
22	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
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27	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
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30	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
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33	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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39	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
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1			should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
2				
3	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
4				
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7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
8				
9				
10	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
11				
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13		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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16 **Methods: Data collection, management, and analysis**

17				
18	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
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23		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
24				
25				
26	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
27				
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30	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
31				
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33		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
34				
35		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
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38 **Methods: Monitoring**

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1	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
2				
3				
4		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
5				
6				
7	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
8				
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
11				
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14	Ethics and dissemination			
15	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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18	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
19				
20				
21	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
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24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
25				
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27	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
28				
29	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
30				
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32	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
33				
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35	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
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38	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
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1	31b	Authorship eligibility guidelines and any intended use of professional writers	15
2	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
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Appendices

6	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
7				
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9	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
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*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.

Peer review only

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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.

Journal:	<i>BMJ Open</i>
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Secondary Subject Heading:	Global health, Health services research, HIV/AIDS
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Clinical trials < THERAPEUTICS, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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3 **Reducing time to differentiated service delivery for newly-diagnosed people living with**
4 **HIV in Kigali, Rwanda: study protocol for a pilot, unblinded randomized control study.**
5

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25 **Keywords:** HIV; differentiated care; antiretroviral therapy; randomized controlled trial; Rwanda
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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]

30 **Strengths and limitations of this study**

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

46 INTRODUCTION

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

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

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

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

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

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

97 **TABLE 1. Current differentiated care delivery model in Rwanda**

	Standard of care		Differentiated Service Delivery	
	Unstable		Stable A	Stable B
Patient	<ul style="list-style-type: none"> • 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 		<ul style="list-style-type: none"> • Adults on 1st and 2nd line ART with 2 consecutive suppressed viral loads 	<ul style="list-style-type: none"> • 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

98 ART: antiretroviral therapy; TB: tuberculosis

99

100 **METHODS AND ANALYSIS**

101 **Trial design**

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

109 **Study setting**

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

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

127 **Eligibility**

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

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3 131 during 12-month duration of study; 2) pregnant or lactating at time of study enrollment; 3) co-
4 132 infected with active tuberculosis at time of study enrollment; 4) concurrent known severe mental
5 133 health or substance use disorder; 5) unable to provide informed consent.
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10 135 **Interventions**

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12 136 Participants will be randomized within 1 month of ART initiation to one of three arms in a
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14 137 1:1:1 ratio, as follows. *Arm 1: Entry into the DSD model at six months after ART initiation with*
15 138 *one suppressed viral load.* In this arm, participants will have their viral loads measured at 5
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17 139 months after ART initiation. If the viral load is suppressed, they will advance to a spaced out
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19 140 appointment schedule of clinical appointments every six months and ART pick up every three
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21 141 months. *Arm 2: Entry into the DSD model at six months after ART initiation with two suppressed*
22 142 *viral loads.* In this arm, participants will have viral loads measured at 3 and 5 months after ART
23
24 143 initiation. If both are suppressed, they will advance to a spaced-out appointment schedule of
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26 144 clinical appointments every six months and ART pick up every three months. Because patients
27
28 145 are expected to be on a dolutegravir-based regimen, we anticipate that those adherent to ART
29
30 146 will have achieved viral suppression within 3 months of ART initiation. *Arm 3: Usual care.* In
31
32 147 this arm, participants will have their viral loads measured at 5 months, but will continue on an
33
34 148 appointment schedule of clinical appointments every three months and ART pick up monthly.

34 149 For participants in the intervention arms, the decision to advance patients to a DSD schedule
35
36 150 is primarily contingent on their viral load measurements at three and/or five months. Health care
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38 151 providers at the health facilities may determine that patients are not eligible for a spaced-out
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40 152 appointment schedule based on clinical assessment. For example, individuals randomized to one
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42 153 of the intervention arms, but who subsequently become ineligible for a DSD schedule because of
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44 154 pregnancy will not be permitted to continue in the DSD schedule and will cross to the usual care
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46 155 arm. Participants in the usual care arm will not be eligible for advancement to a DSD schedule
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48 156 until the study ends, however, those in the intervention arms may choose to attend appointments
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50 157 more frequently if agreed to by their clinician.

50 158 Before the study begins enrollment, staff at participating health facilities will receive training
51
52 159 on the study protocol including eligibility criteria, study design and appointment schedules for
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54 160 the three arms. Throughout the study, the research team will regularly communicate with health
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56 161 facility staff to ensure that eligible study participants in the intervention arms advance to a

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3 162 spaced-out appointment schedule. The study team will review participant medical files to assess
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5 163 fidelity to the appointment schedule. While appointment schedules will be dictated by the study
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7 164 protocol, all other clinical treatments will be at the discretion of health facility clinicians.
8
9 165 Following the trial, participants will continue in regular HIV care at their health facility.

10 166

11 167 **Outcomes**

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13 168 To explore the impact of less frequent appointments and virologic monitoring on patient
14
15 169 outcomes, we will measure viral suppression (primary efficacy outcome) and appointment
16
17 170 attendance (secondary efficacy outcome). Viral suppression will be measured as the proportion
18
19 171 of participants in each arm who achieve viral suppression (viral load <200 copies/ml, based on
20
21 172 current Rwandan guidelines) at 12 months after ART initiation. Appointment attendance will
22
23 173 primarily be measured as the proportion of participants who attend all clinical visits over the first
24
25 174 12 months after ART initiation, by reviewing participant medical records; we will also measure
26
27 175 this outcome as the overall proportion of scheduled visits attended. Patients at study health
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29 176 centers who do not attend a scheduled appointment are called the next day to reschedule. If
30
31 177 unsuccessful, appointments are considered missed; however, outreach efforts continue to be
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33 178 made.

34 179 Feasibility of an early spaced-out appointment schedule and less frequent virologic
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36 180 monitoring will also be examined using process measures including proportion eligible,
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38 181 consented, randomized, the proportion of participants attending appointments in each arm, and
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40 182 cost measures. We will also conduct structured interviews with health facility staff at the end of
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42 183 the study to determine feasibility of implementing this intervention at a larger scale.

43 184 Acceptability of an early spaced-out appointment schedule and less frequent virologic
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45 185 monitoring will be measured through surveys of satisfaction with health care [18,19] as well as
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47 186 structured qualitative interviews with patients and health facility staff in all arms to understand
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49 187 attitudes towards and satisfaction with various appointment schedules, as well as a review of
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51 188 adverse event logs.

52 189 We will also measure the following tertiary outcomes:

- 53 190 ● Changes in ART adherence will be collected using 7- and 30-day self-reported ART
54 191 adherence measures at study entry, 6- and 12-months after ART initiation.

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3 192 ● Changes in participant quality of life will be measured by the EuroQOL-5 Dimension-5
4 193 Levels (EQ-5D-5L),[20] which measures self-rated problems in 5 domains (mobility,
5 194 self-care, usual activities, pain/discomfort and anxiety/depression) as well as self-rated
6 195 health. We will collect and report changes in quality of life at study entry, 6- and 12-
7 196 months after ART initiation.
- 8 197 ● Changes in enacted, internalized, and anticipated stigma will be measured using a
9 198 modified version of the HIV stigma scale [19] as well as the HIV/AIDS Stigma
10 199 Instrument-PLWA (HASI-P) Scale.[21] We will measure stigma at study entry, 6- and
11 200 12-months after ART initiation.
- 12 201 ● Changes in participant health-related expenditures will be measured at study entry, 6- and
13 202 12-months after ART initiation.
- 14 203

204 STUDY PROCEDURES

205 Recruitment

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

215 216 Study timeline

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

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

229

230 **TABLE 2. Schedule of health center and research visits.**

TIMEPOINT (Month)	Health center and research visits after ART initiation (months)											
	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)												
	●					●						●

231 ART: antiretroviral therapy; DSD: differentiated care delivery

232

233 **Informed consent**

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

241

242 **Randomization**

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3 243 At study entry, participants will be randomized to one of three study arms. To ensure equal
4 244 distribution of key factors among randomization arms, we will stratify randomization by age
5 245 group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure
6 246 comparison groups of approximately equal size. Randomization will be computer generated,
7 247 occur in blocks of 6 with 1:1:1 allocation across study arms.

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11 248 To ensure concealment of allocation, a centrally-located data manager will generate the
12 249 allocation sequence and store the sequence in a password-protected file. Since the intervention is
13 250 not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The
14 251 allocation sequence will be generated using the Proc Plan function in SAS (9.4). Upon
15 252 enrollment in the study, research staff will use the randomization function in REDCap (Research
16 253 Electronic Data Capture, v10.0.16, 2020, Vanderbilt University) to assign participants to study
17 254 arms. Because this study is testing the effect of different appointment schedules, it is not feasible
18 255 to blind participants or study personnel, and thus allocation will not be concealed from staff or
19 256 participants.

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28 258 **Data collection**

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30 259 Data will be collected through participant interviews, laboratory tests and medical record
31 260 review. Research staff will be trained in systematic data collection by interview. Interviews will
32 261 be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime
33 262 protocols will be implemented in the event of internet outage. Medical records will be reviewed
34 263 at the end of every study visit, with data entered directly into REDCap. Venous blood specimens
35 264 for clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several
36 265 subsequent visits during the study. Results will be provided to clinical staff at health facilities,
37 266 who will input them into the medical record and report them to participants, consistent with
38 267 routine clinical practices. Viral load measurements will be performed using the Abbott Allinity
39 268 m instrument, with a lower limit of detection of 20 copies/ml. No genetic or molecular analyses
40 269 will be performed; specimens will not be stored for future use.

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51 271 **Analytic approach**

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53 272 We expect to enroll 90 participants into this study. This pilot study is designed to test
54 273 feasibility and acceptability and is thus not powered for hypothesis testing. Sample size was

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3 274 determined based on available resources for conducting the study. The primary analyses will be
4
5 275 by intention to treat.

6 276 Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the
7
8 277 data, examining frequencies, means, medians and ranges to identify any systematic or logical
9
10 278 errors. As this is a pilot study, analyses will be descriptive in nature. Validated instruments will
11
12 279 be coded according to respective scoring instructions. Feasibility will be examined using
13
14 280 descriptive analyses to describe process measures including proportion eligible, consented,
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16 281 randomized, the proportion of participants attending appointments in each arm, and cost
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18 282 measurements. We will also conduct thematic analysis of qualitative, structured interviews to
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20 283 determine intervention acceptability of less intensive DSD models as well as feasibility of
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22 284 implementing this intervention at a larger scale.

23 285 For the outcomes of viral suppression and appointment adherence, the primary analysis will
24
25 286 be intention to treat including all randomized participants, with those who are missing outcome
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27 287 data considered treatment failures. We will first compare study arms with respect to the
28
29 288 proportions of patients achieving viral suppression and attending all clinical and pharmacy visits
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31 289 using chi-square tests. We will then use logistic regression to estimate odds ratios and associated
32
33 290 95% confidence intervals for the effect of each intervention arm compared to the control,
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35 291 adjusting for key baseline covariates that are imbalanced between groups. Because of the small
36
37 292 number of participants we anticipate enrolling in this pilot study, we will not be sufficiently
38
39 293 powered to detect statistically significant differences in outcomes. However, the findings
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41 294 obtained from this study will provide key results on intervention feasibility and guide a future,
42
43 295 larger study to test intervention efficacy.

44 296 Due to the pilot nature of this study, relatively short duration, and small planned enrollment
45
46 297 size, we do not plan on conducting interim analyses. In secondary analyses, we will examine
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48 298 outcomes of viral suppression and appointment attendance using a per-protocol approach. We
49
50 299 will also compare statistical results using a dataset with imputed values and the dataset that drops
51
52 300 missing values, guiding our interpretation of the impact of missing data on findings, as well as
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54 301 our interpretation of overall results. Additional sub-analyses will examine outcomes separately
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56 302 among subgroups of interest (i.e. men, young patients, early defaulters).

57 303

58 304 **Data management**

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3 305 In accordance with Rwandan research regulations, all personally identifying information,
4 306 including participant names and contact information, will be collected using a locally-stored,
5 307 password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g.
6 308 range checks, logical dates) and store interview, medical record and laboratory data. No
7 309 identifying information will be collected in REDCap. Only research investigators and staff will
8 310 have access to study databases. Data quality will be promoted through training research staff to
9 311 uniformly collect and enter data and by periodic data quality monitoring.
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17 313 **Confidentiality**

18 314 The following measures will be utilized to protect participant confidentiality: All paper study
19 315 records (i.e. informed consent documents) will be kept in locked file cabinets with access limited
20 316 to study staff. In accordance with Rwandan research regulations, all personally identifying
21 317 information, including participant names and contact information, will be collected using a
22 318 locally-stored, password-protected, encrypted database. REDCap data will not include any name-
23 319 based or identifying information. Study databases will be maintained on encrypted, password-
24 320 protected computers and servers to which only study staff will have access. To prevent linking of
25 321 sensitive material to participants' personal identifiers, we will utilize separate "name-based" and
26 322 "ID-based" systems. For any paper forms, all documents that have patient identifiers (e.g.
27 323 consent forms, locator forms) will be filed together. Any files that do not include identifying
28 324 information or signatures will only use participants' unique, study-specific IDs (rather than
29 325 names) and will be filed separately from name-based documents. There will only be one
30 326 electronic document that links participants' names to their study IDs, stored on a local,
31 327 password-protected, encrypted server. Publication or presentation of study results will not
32 328 identify subjects.
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46 330 **Study oversight**

47 331 This is a pilot study of approximately 90 participants being conducted to test feasibility and
48 332 acceptability of a modified appointment schedule. This is a low risk study that involves pilot
49 333 testing an intervention that will enroll a relatively small number of participants, and it is unlikely
50 334 that study participants will experience adverse reactions related to study participation. Therefore
51 335 there will not be a Data Safety and Monitoring Board. The study team, consisting of the PI, co-
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3 336 investigators, and research staff, meet weekly to review study progress, including review of
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5 337 adverse events. If adverse events occur, the PI will act to minimize their impact and ensure the
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7 338 adverse event is reported to the responsible authorities in a timely manner as required. There is
8
9 339 no coordinating center or steering committee. This pilot trial will not be audited.

10 340

11 341 **Adverse event reporting and harms**

12 342 The PI, together with the study team, will be responsible for regularly monitoring data and
13 343 safety, specifically assessing for adverse events and breach of confidentiality. If adverse events
14 344 occur, the study team will: 1) identify the concern, 2) activate the appropriate response to
15 345 minimize the adverse event, and 3) ensure the adverse event is reported to the responsible
16 346 authority in a timely manner. If patients have a medical or psychiatric decompensation during the
17 347 study, research staff will inform their direct supervisor, who will assess the patient in-person, and
18 348 will notify the PI or co-investigators immediately. Based on clinical judgment, study participants
19 349 will be referred to psychiatric or medical consultation in the health facility or referred for
20 350 emergency care. The study database will be secured with encryption and password protection,
21 351 and the study team will monitor the database for potential breaches of confidentiality.

22 352 All adverse events will be compiled monthly. Unanticipated, non-serious adverse events will
23 353 be documented and reported by the PI to the Albert Einstein College of Medicine IRB and the
24 354 Rwanda National Ethics Committee within 30 days. Serious adverse events will be reported by
25 355 the PI to the Albert Einstein College of Medicine IRB and Rwanda National Ethics Committee
26 356 within 48 hours by phone, email, or fax.

27 357

28 358 **Discussion**

29 359 This trial will pilot test reducing the time to DSD from 12 to 6 months as well as reducing the
30 360 number of suppressed viral loads required to enter DSD from two to one, compared to usual care.
31 361 If found feasible and acceptable, this approach could reduce inconvenience and stigma for
32 362 newly-diagnosed PLHIV as well as lower the medical resources required for treatment.

33 363 This study may face potential limitations. Participants in the intervention arm with two viral
34 364 load measurements effectively have twice as many opportunities to not be virally suppressed,
35 365 and therefore may be less likely to advance to DSD. Similarly, participants will advance to DSD
36 366 at the discretion of treating clinicians. This may bias the study findings if participants in the

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3 367 intervention arms effectively follow the standard of care, and may result in less power to detect
4 368 differences between the study arms in the intention to treat analysis. Nonetheless, the study will
5 369 provide important feasibility and acceptability data on the optimal number of viral load
6 370 measurements needed to determine clinical stability. Blinding will not be feasible for this study,
7 371 which may bias the study findings. Finally, we will be enrolling patients who receive care at
8 372 health facilities located in or near the capital of a country with a highly functional HIV care
9 373 service delivery system and with a lower HIV prevalence than in much of southern Africa. This
10 374 may limit the generalizability of our findings.

11 375 DSD models, including less frequent appointment schedules, are increasingly being adopted
12 376 across HIV care settings globally, and are acceptable to patients and cost-effective.[4-8, 22-23] A
13 377 key question in implementing DSD models is determining at what point patients receiving HIV
14 378 care can be considered clinically stable. By testing the effect of reduced time to DSD as well as
15 379 fewer viral load measurements prior to entering DSD, this study will provide key parameters for
16 380 a subsequent, larger efficacy trial, and provide practical data for HIV program implementation in
17 381 Rwanda as well as globally.

18 382

19 383 **Patient and public involvement**

20 384 The design of this study was informed by findings of formative, qualitative research
21 385 conducted with patients at study health centers,[15] clinical experiences of several of the authors,
22 386 along with input from public health and clinical leaders in Rwanda. The research questions and
23 387 design were reviewed by investigators with expertise in HIV health services delivery and
24 388 infectious diseases, along with input from an advisory committee consisting of leadership from
25 389 study health centers as well as the Rwanda Biomedical Center, the nation's central health
26 390 implementation agency.

27 391

28 392 **ETHICS AND DISSEMINATION**

29 393 This clinical trial was approved by the institutional review board (IRB) of Albert Einstein
30 394 College of Medicine and by the Rwanda National Ethics Committee and is registered on
31 395 www.clinicaltrials.gov [NCT04567693].

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3 396 By testing the effect of reduced time to DSD as well as fewer viral load measurements prior
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5 397 to entering DSD, this study will provide key parameters for a subsequent, larger efficacy trial,
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7 398 and provide practical data for HIV program implementation in Rwanda as well as globally.
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9 399 We will disseminate study findings through presentations at scientific conferences, publications
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11 400 in peer-reviewed journals, and presentations to patients, providers and key institutional
12
13 401 stakeholders. Study findings will be reported in accordance with the Consolidated Standards of
14
15 402 Reporting Trials (CONSORT) standards.

16 403

17 404 **TRIAL STATUS**

18
19 405 The current protocol is version 1.4, dated 28 September 2020. Any important protocol
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21 406 amendments will be communicated immediately to the responsible ethical committees and will
22
23 407 be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is
24
25 408 expected to continue until August 2021, with follow-up continuing until August 2022.

26 409

27 28 410 **AUTHOR'S CONTRIBUTIONS**

29
30 411 JR is the Principal Investigator; he conceived the study, led the proposal and protocol
31
32 412 development. SH, CI, FU, AM, BM, GM, and KA contributed to study design and to
33
34 413 development of the proposal. ER, DSH, PM, and MY provided additional input to study design.
35
36 414 CZ provided statistical support. All authors read and approved the final manuscript.

37 415

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39
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47
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53
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55
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1
2
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4
5 427 +1.718.920.4321. The study sponsor and funder have no role in study design; collection,
6
7 428 management, analysis, and interpretation of data; writing of the report; and the decision to
8
9 429 submit the report for publication.

10 430

11 431 **COMPETING INTERESTS**

12 432 The authors declare that they have no competing interests or conflicts of interest to disclose.

13 433

14 434 **DATA AVAILABILITY**

15 435 The final trial dataset will not be released publicly based on policies of the Rwandan Ministry
16 436 of Health. In August 2024 (two years after the conclusion of data collection), the dataset can be
17 437 shared on upon written request to, and after review and approval by, Dr. Gad Murenzi
18 438 (gadcollins@gmail.com).

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For peer review only

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.

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4 As part of this study we will review your medical records and put the information we collect in
5 our research records.
6

7 **How many people will take part in the research study?**

8 You will be one of about **90** people who will be participating in this study.
9

10 **Genetic Testing**

11 This study will not involve genetic research or genetic testing.
12

13 **Specimen Banking (Future Use and Storage)**

14 We will destroy the specimens and information about you when the study is complete.
15 Information about you will be kept as long as required by regulations and institutional policy,
16 but will not be used for future studies.
17

18 **Information Banking (Future Use and Storage)**

19 Information about you will be kept as long as required by regulations and institutional policy,
20 but will not be used for future studies.
21

22 **Will I be paid for being in this research study?**

23 You will receive a total of RWF 24,000 for 3 study visits. You will receive RWF 8,000 in cash at
24 the end of each visit. If you choose to withdraw from the study before all visits are completed,
25 you will be paid only for the visits you completed.
26

27 **Will it cost me anything to participate in this study?**

28 Taking part in this study will not involve added costs to you. All care will be given free of charge
29 as per Government of Rwanda policies.
30

31 **Confidentiality**

32 The researchers and study staff follow US federal and state laws as well as Government of
33 Rwanda laws to protect your privacy. This part of the consent form tells you what information
34 about you may be used and shared in the research described in this form. You do not have to
35 sign this form but, if you do not, you may not participate in the research.
36

37 The health information that we may use or disclose for the research described in this form
38 includes information from your entire medical record, such as your name, phone number, email,
39 medical diagnoses, dates, test results, social security number, medical record numbers, etc.
40

41 Your information and research records will be kept confidential. Your study information will be
42 kept as long as they are useful for the research described in this form.
43

44 The only people who can see your research records are:

- 45 • Researchers and other individuals who work with the researchers
- 46 • Organizations and institutions involved in this research, including those that fund the
47 research, if applicable
- 48 • Groups that review research such as central reviewers, Institutional Review Boards, the
49 Office for Human Research Protections, the US Food and Drug Administration, data
50 coordinating centers, and domestic and foreign agencies that regulate research.
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3 The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the
4 study is being done correctly. The information covered under this form may no longer be
5 protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who
6 receive your health information may share your information with others without your additional
7 permission. All of these groups have been asked to keep your information confidential.
8

9 Medical information collected during the research, such as test results, may be entered into your
10 medical record and will be available to clinicians and other staff who provide care to you.
11

12 To maintain the integrity of this research study, you generally will not have access to your
13 research-related personal health information. If it is necessary for your care, your research-
14 related health information will be provided to you or your physician.
15

16 **Are there any times you would not keep my data confidential?**

17 If you give us information that suggests that your child or any other child is being abused, we
18 are required by law to report that information to the Government of Rwanda agencies in charge
19 of child protection. Reporting this information may put you, your family, or others who are
20 involved at risk of questioning and legal action by the authorities.
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23 If you give us information that you are in danger of hurting yourself, hurting someone else, or
24 being hurt by someone else, we might not be able to keep this information confidential, and
25 might need to share this information with social work or mental health staff at the health center
26 in order to help you.
27

28 **Certificate of Confidentiality**

29 As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the
30 National Institutes of Health, which is funding this study. If information from this study were
31 requested or subpoenaed by government agencies or the courts, we would use the Certificate
32 to attempt to legally refuse to provide that information. These requests are rare – in only a few
33 cases did researchers have to use the Certificate, and it was honored most of the time, but not
34 every time. There are several kinds of situations to which the Certificate does not apply. For
35 example, we are still required to report child abuse and some diseases, and we must make data
36 available to the government for review or evaluation of our research. The Certificate does not
37 prevent you or a member of your family from voluntarily sharing information. Similarly, if an
38 insurer, employer, or other person obtains your written consent to receive research information,
39 then the researchers may not use the Certificate to withhold that information.
40
41

42 **Are there any risks to me?**

43 As part of this study you may have fewer regularly scheduled visits to the health center, which
44 may put you at risk of worse adherence to your medications or appointments, or make you feel
45 like you have less support from the health center.
46

47 A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of
48 privacy means having your personal information shared with someone who is not on the study
49 team and was not supposed to see or know about your information. The study team plans to
50 protect your privacy – see the Confidentiality section above for details.
51

52 **Questionnaire**

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

1	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
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5	Methods: Participants, interventions, and outcomes			
6	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
7				
8				
9	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
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12	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
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15		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
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18		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,11
19				
20				
21		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
22	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
23				
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27	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
28				
29				
30	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
31				
32				
33	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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39	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
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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

1	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
2				
3				
4		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
5				
6				
7	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
8				
9				
10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
11				
12				
13				
14	Ethics and dissemination			
15	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
16				
17				
18	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
19				
20				
21	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
22				
23				
24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
25				
26				
27	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
28				
29	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
30				
31				
32	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
33				
34				
35	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
36				
37				
38	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
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1	31b	Authorship eligibility guidelines and any intended use of professional writers	16
2	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
3			
4			

Appendices

6	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
8				
9	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
10				
11				

*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.

Peer review only

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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3 **Reducing time to differentiated service delivery for newly-diagnosed people living with**
4 **HIV in Kigali, Rwanda: study protocol for a pilot, unblinded, randomized controlled study.**
5

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

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]

30 **Strengths and limitations of this study**

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

46 INTRODUCTION

47 With the goal of ending the HIV pandemic, the UNAIDS “90-90-90” targets for 2020 are that
48 90% of all people living with HIV (PLHIV) know their HIV status, 90% of people with
49 diagnosed HIV infection receive sustained antiretroviral therapy (ART), and 90% of all people
50 receiving ART achieve viral suppression. [1] To this end, in 2015 the World Health Organization
51 (WHO) recommended in its Treat All guidelines that all PLHIV initiate ART as quickly as
52 possible after diagnosis.[2] Since implementation of its Treat All policy in 2016, Rwanda has
53 nearly achieved UNAIDS 90-90-90 targets,[3] yet groups including men and younger PLHIV
54 remain at higher risk of poorer outcomes. Reducing barriers to initiating and adhering to therapy
55 is thus paramount to ensuring all PLHIV in Rwanda succeed in HIV therapy.

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

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

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

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

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

97 **TABLE 1. Current differentiated care delivery model in Rwanda**

	Standard of care	Differentiated Service Delivery	
	Unstable	Stable A	Stable B
Patient	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Adults on 1st and 2nd line ART with 2 consecutive suppressed viral loads 	<ul style="list-style-type: none"> • 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

98 ART: antiretroviral therapy; TB: tuberculosis

99

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

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3 131 during 12-month duration of study; 2) pregnant or lactating at time of study enrollment; 3) co-
4 132 infected with active tuberculosis at time of study enrollment; 4) concurrent known severe mental
5 133 health or substance use disorder; 5) unable to provide informed consent.
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134

10 135 **Interventions**

11
12 136 Participants will be randomized within 1 month of ART initiation to one of three arms in a
13
14 137 1:1:1 ratio, as follows. *Arm 1: Entry into the DSD model at six months after ART initiation with*
15 138 *one suppressed viral load.* In this arm, participants will have their viral loads measured at 5
16
17 139 months after ART initiation. If the viral load is suppressed, they will advance to a spaced out
18
19 140 appointment schedule of clinical appointments every six months and ART pick up every three
20
21 141 months. *Arm 2: Entry into the DSD model at six months after ART initiation with two suppressed*
22 142 *viral loads.* In this arm, participants will have viral loads measured at 3 and 5 months after ART
23
24 143 initiation. If both are suppressed, they will advance to a spaced-out appointment schedule of
25
26 144 clinical appointments every six months and ART pick up every three months. Because patients
27
28 145 are expected to be on a dolutegravir-based regimen, we anticipate that those adherent to ART
29
30 146 will have achieved viral suppression within 3 months of ART initiation. *Arm 3: Usual care.* In
31
32 147 this arm, participants will have their viral loads measured at 5 months, but will continue on an
33
34 148 appointment schedule of clinical appointments every three months and ART pick up monthly.

34 149 For participants in the intervention arms, the decision to advance patients to a DSD schedule
35
36 150 is primarily contingent on their viral load measurements at three and/or five months. However,
37
38 151 health care providers at the health facilities may determine that patients are not eligible for a
39
40 152 spaced-out appointment schedule based on overall clinical assessment and override the study
41
42 153 assignment. For example, individuals randomized to one of the intervention arms, but who
43
44 154 subsequently become ineligible for a DSD schedule because of pregnancy will not be permitted
45
46 155 to continue in the DSD schedule and will cross to the usual care arm. Participants in the usual
47
48 156 care arm will not be eligible for advancement to a DSD schedule until the study ends, however,
49
50 157 those in the intervention arms may choose to attend appointments more frequently if agreed to by
51
52 158 their clinician. All instances in which health center staff determine that participants cannot
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54 159 advance to or continue in a spaced-out appointment schedule, including the reason for the change
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60 160 and whether it was initiated by the clinician or patient, will be recorded.

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3 161 Before the study begins enrollment, staff at participating health facilities will receive training
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5 162 on the study protocol including eligibility criteria, study design and appointment schedules for
6
7 163 the three arms. Throughout the study, the research team will regularly communicate with health
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9 164 facility staff to ensure that eligible study participants in the intervention arms advance to a
10
11 165 spaced-out appointment schedule. The study team will review participant medical files to assess
12
13 166 fidelity to the appointment schedule. While appointment schedules will be dictated by the study
14
15 167 protocol, all other clinical treatments will be at the discretion of health facility clinicians.
16
17 168 Following the trial, participants will continue in regular HIV care at their health facility; those in
18
19 169 the usual care arm who were virally suppressed on preceding measurements will be eligible for
20
21 170 advancement to a DSD schedule at this time.

22 171

23 172 **Outcomes**

24 173 To explore the impact of less frequent appointments and virologic monitoring on patient
25
26 174 outcomes, we will measure viral suppression (primary efficacy outcome) and appointment
27
28 175 attendance (secondary efficacy outcome). Viral suppression will be measured as the proportion
29
30 176 of participants in each arm who achieve viral suppression (viral load <200 copies/ml, based on
31
32 177 current Rwandan guidelines) at 12 months after ART initiation. Appointment attendance will
33
34 178 primarily be measured as the proportion of participants who attend all scheduled clinical and
35
36 179 pharmacy visits over the first 12 months after ART initiation (11 in arms 1 and 2; 16 in arm 3),
37
38 180 by reviewing participant medical records; we will also measure this outcome as the overall
39
40 181 proportion of scheduled visits attended. Patients at study health centers who do not attend a
41
42 182 scheduled appointment are called the next day to reschedule. If unsuccessful, appointments are
43
44 183 considered missed; however, outreach efforts continue to be made.

45 184 Feasibility of an early spaced-out appointment schedule and less frequent virologic
46
47 185 monitoring will also be examined using process measures including proportion eligible,
48
49 186 consented, randomized, the proportion of participants attending appointments in each arm, and
50
51 187 cost measures. We will also conduct structured interviews with health facility staff at the end of
52
53 188 the study to determine feasibility of implementing this intervention at a larger scale.

54 189 Acceptability of an early spaced-out appointment schedule and less frequent virologic
55
56 190 monitoring will be measured through: 1) surveys of satisfaction with health care [18,19]; 2)
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58 191 structured qualitative interviews with patients and health facility staff in all arms to understand

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3 192 attitudes towards and satisfaction with various appointment schedules; 3) review of instances in
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5 193 which health center clinicians override the experimental assignment; and 4) review of adverse
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7 194 event logs.

8 195 We will also measure within-group change over time and differences between groups for the
9
10 196 following tertiary outcomes:

- 11
12 197 ● ART adherence will be collected using 7- and 30-day self-reported ART adherence
13
14 198 measures at study entry, 6- and 12-months after ART initiation.
- 15 199 ● Participant quality of life will be measured by the EuroQOL-5 Dimension-5 Levels (EQ-
16
17 200 5D-5L),[20] which measures self-rated problems in 5 domains (mobility, self-care, usual
18
19 201 activities, pain/discomfort and anxiety/depression) as well as self-rated health. We will
20
21 202 collect and report changes in quality of life at study entry, 6- and 12-months after ART
22
23 203 initiation.
- 24 204 ● Enacted, internalized, and anticipated stigma will be measured using a modified version
25
26 205 of the HIV stigma scale [19] as well as the HIV/AIDS Stigma Instrument-PLWA (HASI-
27
28 206 P) Scale.[21] We will measure stigma at study entry, 6- and 12-months after ART
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30 207 initiation.
- 31 208 ● Participant health-related expenditures will be measured at study entry, 6- and 12-months
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33 209 after ART initiation.

34 210

35 36 211 **STUDY PROCEDURES**

37 38 212 **Recruitment**

39
40 213 Active recruitment will occur via health facility nurses who will inform potentially eligible
41
42 214 patients about the study during their routine appointments. Each week a designated health facility
43
44 215 staff member will provide the research assistant with a list of patients who indicated interest in
45
46 216 participating and who meet eligibility criteria (i.e. newly-diagnosed, not pregnant or lactating,
47
48 217 without severe mental health conditions). Passive recruitment will occur through research
49
50 218 assistants who will also make general announcements about the study during morning health
51
52 219 education sessions at health facilities, and be available to answer questions and collect interested
53
54 220 patient's contact information. Interested patients will be screened by study staff for eligibility,
55
56 221 and if eligible will be offered enrollment in the study.

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223 Study timeline

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

237 **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)												
	●					●						●

238 ART: antiretroviral therapy; DSD: differentiated care delivery

240 Informed consent

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

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3 243 will be obtained from all participants (Supplemental File 1, Model consent form). Participants
4 244 aged 15-18 will provide assent with informed consent obtained from their parent or legal
5 245 guardian. Research staff will read the informed consent document to participants in its entirety;
6 246 participants unable to sign their name will be permitted to sign with an "X." No additional
7 247 consent provisions are required for collection and use of participant medical record data and
8 248 biological specimens in this study.
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250 **Randomization**

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16
17 251 At study entry, participants will be randomized to one of three study arms. To ensure equal
18 252 distribution of key factors among randomization arms, we will stratify randomization by age
19 253 group (younger or older than 24 years) and health facility. We will randomize in blocks to ensure
20 254 comparison groups of approximately equal size. Randomization will be computer generated,
21 255 occur in blocks of 6 with 1:1:1 allocation across study arms.
22
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25
26 256 To ensure concealment of allocation, a centrally-located data manager will generate the
27 257 allocation sequence and store the sequence in a password-protected file. Since the intervention is
28 258 not blinded, we will use block size of 6 to prevent anticipation of treatment arm assignment. The
29 259 allocation sequence will be generated using the Proc Plan function in SAS (9.4). Upon
30 260 enrollment in the study, research staff will use the randomization function in REDCap (Research
31 261 Electronic Data Capture, v10.0.16, 2020, Vanderbilt University) to assign participants to study
32 262 arms. Because this study is examining the effect of different appointment schedules, it is not
33 263 feasible to blind participants or study personnel, and thus allocation will not be concealed from
34 264 staff or participants.
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265

43 266 **Data collection**

44
45 267 Data will be collected through participant interviews, laboratory tests and medical record
46 268 review. Research staff will be trained in systematic data collection by interview. Interviews will
47 269 be conducted in Kinyarwanda by staff with responses entered directly into REDCap. Downtime
48 270 protocols will be implemented in the event of internet outage. Medical records will be reviewed
49 271 at the end of every study visit, with data entered directly into REDCap. Venous blood specimens
50 272 for clinical monitoring (e.g. CD4 count, viral load) will be collected at study entry and at several
51 273 subsequent visits during the study. Results will be provided to clinical staff at health facilities,
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3 274 who will input them into the medical record and report them to participants, consistent with
4
5 275 routine clinical practices. Viral load measurements will be performed using the Abbott Allinity
6
7 276 m instrument, with a lower limit of detection of 20 copies/ml. No genetic or molecular analyses
8
9 277 will be performed; specimens will not be stored for future use.

10 278

11 279 **Analytic approach**

12
13 280 We expect to enroll 90 participants into this study. This pilot study is designed to test
14
15 281 feasibility and acceptability and is thus not powered for hypothesis testing. Sample size was
16
17 282 determined based on available resources for conducting the study. The primary analyses will be
18
19 283 by intention to treat.

20 284 Data obtained through REDCap will be imported into SAS version 9.4. We will first clean the
21
22 285 data, examining frequencies, means, medians and ranges to identify any systematic or logical
23
24 286 errors. As this is a pilot study, analyses will be descriptive in nature. Validated instruments will
25
26 287 be coded according to respective scoring instructions. Feasibility will be examined using
27
28 288 descriptive analyses to describe process measures including proportion eligible, consented,
29
30 289 randomized, the proportion of participants attending appointments in each arm, and cost
31
32 290 measurements. We will also conduct thematic analysis of qualitative, structured interviews to
33
34 291 determine intervention acceptability of less intensive DSD models as well as feasibility of
35
36 292 implementing this intervention at a larger scale.

37 293 For the outcomes of viral suppression and appointment adherence, the primary analysis will
38
39 294 be intention to treat including all randomized participants, with those who are missing outcome
40
41 295 data considered treatment failures. We will first compare study arms with respect to the
42
43 296 proportions of patients achieving viral suppression and attending all clinical and pharmacy visits
44
45 297 using chi-square tests. We will then use logistic regression to estimate odds ratios and associated
46
47 298 95% confidence intervals for the effect of each intervention arm compared to the control,
48
49 299 adjusting for key baseline covariates that are imbalanced between groups. Because of the small
50
51 300 number of participants we anticipate enrolling in this pilot study, we will not be sufficiently
52
53 301 powered to detect statistically significant differences in outcomes. However, the findings
54
55 302 obtained from this study will provide key results on intervention feasibility and guide a future,
56
57 303 larger study to test intervention efficacy.

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3 304 Due to the pilot nature of this study, relatively short duration, and small planned enrollment
4
5 305 size, we do not plan on conducting interim analyses. In secondary analyses, we will examine
6
7 306 outcomes of viral suppression and appointment attendance using a per-protocol approach. We
8
9 307 will also compare statistical results using a dataset with imputed values and the dataset that drops
10
11 308 missing values, guiding our interpretation of the impact of missing data on findings, as well as
12
13 309 our interpretation of overall results. Moreover, because outcome data may be missing for
14
15 310 different reasons, we will document reasons for missingness to the degree possible to inform
16
17 311 these additional analyses. For example, while the number of deaths is anticipated to be small, we
18
19 312 will conduct analyses both including and excluding participants who died to understand the
20
21 313 potential impact of death on results. Additional sub-analyses will examine outcomes separately
22
23 314 among subgroups of interest (i.e. men, young patients, early defaulters) though these may be
24
25 315 limited by the small size of some subgroups.
26

27 316 **Data management**

28 317 In accordance with Rwandan research regulations, all personally identifying information,
29
30 318 including participant names and contact information, will be collected using a locally-stored,
31
32 319 password-protected, encrypted database. REDCap will be used to securely collect, validate (e.g.
33
34 320 range checks, logical dates) and store interview, medical record and laboratory data. No
35
36 321 identifying information will be collected in REDCap. Only research investigators and staff will
37
38 322 have access to study databases. Data quality will be promoted through training research staff to
39
40 323 uniformly collect and enter data and by periodic data quality monitoring.
41

42 324 **Confidentiality**

43 325 The following measures will be utilized to protect participant confidentiality: All paper study
44
45 326 records (i.e. informed consent documents) will be kept in locked file cabinets with access limited
46
47 327 to study staff. In accordance with Rwandan research regulations, all personally identifying
48
49 328 information, including participant names and contact information, will be collected using a
50
51 329 locally-stored, password-protected, encrypted database. REDCap data will not include any name-
52
53 330 based or identifying information. Study databases will be maintained on encrypted, password-
54
55 331 protected computers and servers to which only study staff will have access. To prevent linking of
56
57 332 sensitive material to participants' personal identifiers, we will utilize separate "name-based" and
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3 335 “ID-based” systems. For any paper forms, all documents that have patient identifiers (e.g.
4 336 consent forms, locator forms) will be filed together. Any files that do not include identifying
5 337 information or signatures will only use participants’ unique, study-specific IDs (rather than
6 338 names) and will be filed separately from name-based documents. There will only be one
7 339 electronic document that links participants’ names to their study IDs, stored on a local,
8 340 password-protected, encrypted server. Publication or presentation of study results will not
9 341 identify subjects.
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343 **Study oversight**

17
18 344 This is a pilot study of approximately 90 participants being conducted to test feasibility and
19 345 acceptability of a modified appointment schedule. This is a low risk study that involves pilot
20 346 testing an intervention that will enroll a relatively small number of participants, and it is unlikely
21 347 that study participants will experience adverse reactions related to study participation. Therefore
22 348 there will not be a Data Safety and Monitoring Board. The study team, consisting of the PI, co-
23 349 investigators, and research staff, meet weekly to review study progress, including review of
24 350 adverse events. If adverse events occur, the PI will act to minimize their impact and ensure the
25 351 adverse event is reported to the responsible authorities in a timely manner as required. There is
26 352 no coordinating center or steering committee. This pilot trial will not be audited.
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354 **Adverse event reporting and harms**

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36 355 The PI, together with the study team, will be responsible for regularly monitoring data and
37 356 safety, specifically assessing for adverse events and breach of confidentiality. If adverse events
38 357 occur, the study team will: 1) identify the concern, 2) activate the appropriate response to
39 358 minimize the adverse event, and 3) ensure the adverse event is reported to the responsible
40 359 authority in a timely manner. If patients have a medical or psychiatric decompensation during the
41 360 study, research staff will inform their direct supervisor, who will assess the patient in-person, and
42 361 will notify the PI or co-investigators immediately. Based on clinical judgment, study participants
43 362 will be referred to psychiatric or medical consultation in the health facility or referred for
44 363 emergency care. The study database will be secured with encryption and password protection,
45 364 and the study team will monitor the database for potential breaches of confidentiality.
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3 365 All adverse events will be compiled monthly. Unanticipated, non-serious adverse events will
4
5 366 be documented and reported by the PI to the Albert Einstein College of Medicine IRB and the
6
7 367 Rwanda National Ethics Committee within 30 days. Serious adverse events will be reported by
8
9 368 the PI to the Albert Einstein College of Medicine IRB and Rwanda National Ethics Committee
10
11 369 within 48 hours by phone, email, or fax.
12

13 370

14 371 **Discussion**

15 372 This trial will pilot test reducing the time to DSD from 12 to 6 months as well as reducing the
16
17 373 number of suppressed viral loads required to enter DSD from two to one, compared to usual care.
18
19 374 If found feasible and acceptable, this approach could reduce inconvenience and stigma for
20
21 375 newly-diagnosed PLHIV as well as lower the medical resources required for treatment.

22 376 This study may face potential limitations. Participants in the intervention arm with two viral
23
24 377 load measurements effectively have twice as many opportunities to not be virally suppressed,
25
26 378 with viral suppression less likely at 3 compared to 5 months, and therefore may be less likely to
27
28 379 advance to DSD. Similarly, participants will advance to DSD at the discretion of treating
29
30 380 clinicians. This may bias the study findings if participants in the intervention arms effectively
31
32 381 follow the standard of care, and may result in less power to detect differences between the study
33
34 382 arms in the intention to treat analysis. Nonetheless, the study will provide important feasibility
35
36 383 and acceptability data on the optimal number of viral load measurements needed to determine
37
38 384 clinical stability. Because inclusion criteria specify HIV diagnosis within the preceding 6
39
40 385 months, it is possible that participants will have been in care elsewhere and defaulted prior to
41
42 386 enrolling in study health centers, and thus not ART-naïve. While it may not be possible to know
43
44 387 if patients are truly newly-diagnosed, we expect that any early defaulters would be equally
45
46 388 distributed between arms given the randomized nature of this study, and thus would not impact
47
48 389 analysis of outcomes. Blinding will not be feasible for this study, which may bias the study
49
50 390 findings. ART adherence will be measured by self-report, which may imperfectly reflect true
51
52 391 medication adherence. Finally, we will be enrolling patients who receive care at health facilities
53
54 392 located in or near the capital of a country with a highly functional HIV care service delivery
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56 393 system and with a lower HIV prevalence than in much of southern Africa. This may limit the
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58 394 generalizability of our findings.
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3 395 DSD models, including less frequent appointment schedules, are increasingly being adopted
4
5 396 across HIV care settings globally, and are acceptable to patients and cost-effective.[4-8, 22-23] A
6
7 397 key question in implementing DSD models is determining at what point patients receiving HIV
8
9 398 care can be considered clinically stable. By examining the effect of reduced time to DSD as well
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11 399 as fewer viral load measurements prior to entering DSD, this study will provide key parameters
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13 400 for a subsequent, larger efficacy trial, and provide practical data for HIV program
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15 401 implementation in Rwanda as well as globally.
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403 **Patient and public involvement**

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18 404 The design of this study was informed by findings of formative, qualitative research
19
20 405 conducted with patients at study health centers,[15] clinical experiences of several of the authors,
21
22 406 along with input from public health and clinical leaders in Rwanda. The research questions and
23
24 407 design were reviewed by investigators with expertise in HIV health services delivery and
25
26 408 infectious diseases, along with input from an advisory committee consisting of leadership from
27
28 409 study health centers as well as the Rwanda Biomedical Center, the nation's central health
29
30 410 implementation agency.
31

411

412 **ETHICS AND DISSEMINATION**

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34 413 This clinical trial was approved by the institutional review board (IRB) of Albert Einstein
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36 414 College of Medicine and by the Rwanda National Ethics Committee and is registered on
37
38 415 www.clinicaltrials.gov [NCT04567693].

39
40 416 By examining the effect of reduced time to DSD as well as fewer viral load measurements
41
42 417 prior to entering DSD, this study will provide key parameters for a subsequent, larger efficacy
43
44 418 trial, and provide practical data for HIV program implementation in Rwanda as well as globally.
45
46 419 We will disseminate study findings through presentations at scientific conferences, publications
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48 420 in peer-reviewed journals, and presentations to patients, providers and key institutional
49
50 421 stakeholders. Study findings will be reported in accordance with the Consolidated Standards of
51
52 422 Reporting Trials (CONSORT) standards.

423

424 **TRIAL STATUS**

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3 425 The current protocol is version 1.4, dated 28 September 2020. Any important protocol
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5 426 amendments will be communicated immediately to the responsible ethical committees and will
6
7 427 be reported in resulting publications. Recruitment for this trial began on 22 October 2020 and is
8
9 428 expected to continue until August 2021, with follow-up continuing until August 2022.

429

430 **AUTHOR'S CONTRIBUTIONS**

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

435

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448 management, analysis, and interpretation of data; writing of the report; and the decision to
449 submit the report for publication.

450

451 **COMPETING INTERESTS**

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

453

454 **DATA AVAILABILITY**

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2
3 455 The final trial dataset will not be released publicly based on policies of the Rwandan Ministry
4
5 456 of Health. In August 2024 (two years after the conclusion of data collection), the dataset can be
6
7 457 shared on upon written request to, and after review and approval by, Dr. Gad Murenzi
8
9 458 (gadcollins@gmail.com).

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531

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.

1
2
3
4 As part of this study we will review your medical records and put the information we collect in
5 our research records.
6

7 **How many people will take part in the research study?**

8 You will be one of about **90** people who will be participating in this study.
9

10 **Genetic Testing**

11 This study will not involve genetic research or genetic testing.
12

13 **Specimen Banking (Future Use and Storage)**

14 We will destroy the specimens and information about you when the study is complete.
15 Information about you will be kept as long as required by regulations and institutional policy,
16 but will not be used for future studies.
17

18 **Information Banking (Future Use and Storage)**

19 Information about you will be kept as long as required by regulations and institutional policy,
20 but will not be used for future studies.
21

22 **Will I be paid for being in this research study?**

23 You will receive a total of RWF 24,000 for 3 study visits. You will receive RWF 8,000 in cash at
24 the end of each visit. If you choose to withdraw from the study before all visits are completed,
25 you will be paid only for the visits you completed.
26

27 **Will it cost me anything to participate in this study?**

28 Taking part in this study will not involve added costs to you. All care will be given free of charge
29 as per Government of Rwanda policies.
30

31 **Confidentiality**

32 The researchers and study staff follow US federal and state laws as well as Government of
33 Rwanda laws to protect your privacy. This part of the consent form tells you what information
34 about you may be used and shared in the research described in this form. You do not have to
35 sign this form but, if you do not, you may not participate in the research.
36

37 The health information that we may use or disclose for the research described in this form
38 includes information from your entire medical record, such as your name, phone number, email,
39 medical diagnoses, dates, test results, social security number, medical record numbers, etc.
40

41 Your information and research records will be kept confidential. Your study information will be
42 kept as long as they are useful for the research described in this form.
43

44 The only people who can see your research records are:

- 45 • Researchers and other individuals who work with the researchers
- 46 • Organizations and institutions involved in this research, including those that fund the
47 research, if applicable
- 48 • Groups that review research such as central reviewers, Institutional Review Boards, the
49 Office for Human Research Protections, the US Food and Drug Administration, data
50 coordinating centers, and domestic and foreign agencies that regulate research.
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2
3 The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the
4 study is being done correctly. The information covered under this form may no longer be
5 protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who
6 receive your health information may share your information with others without your additional
7 permission. All of these groups have been asked to keep your information confidential.
8

9
10 Medical information collected during the research, such as test results, may be entered into your
11 medical record and will be available to clinicians and other staff who provide care to you.
12

13 To maintain the integrity of this research study, you generally will not have access to your
14 research-related personal health information. If it is necessary for your care, your research-
15 related health information will be provided to you or your physician.
16

17 **Are there any times you would not keep my data confidential?**

18 If you give us information that suggests that your child or any other child is being abused, we
19 are required by law to report that information to the Government of Rwanda agencies in charge
20 of child protection. Reporting this information may put you, your family, or others who are
21 involved at risk of questioning and legal action by the authorities.
22

23 If you give us information that you are in danger of hurting yourself, hurting someone else, or
24 being hurt by someone else, we might not be able to keep this information confidential, and
25 might need to share this information with social work or mental health staff at the health center
26 in order to help you.
27

28 **Certificate of Confidentiality**

29 As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the
30 National Institutes of Health, which is funding this study. If information from this study were
31 requested or subpoenaed by government agencies or the courts, we would use the Certificate
32 to attempt to legally refuse to provide that information. These requests are rare – in only a few
33 cases did researchers have to use the Certificate, and it was honored most of the time, but not
34 every time. There are several kinds of situations to which the Certificate does not apply. For
35 example, we are still required to report child abuse and some diseases, and we must make data
36 available to the government for review or evaluation of our research. The Certificate does not
37 prevent you or a member of your family from voluntarily sharing information. Similarly, if an
38 insurer, employer, or other person obtains your written consent to receive research information,
39 then the researchers may not use the Certificate to withhold that information.
40
41

42 **Are there any risks to me?**

43 As part of this study you may have fewer regularly scheduled visits to the health center, which
44 may put you at risk of worse adherence to your medications or appointments, or make you feel
45 like you have less support from the health center.
46

47 A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of
48 privacy means having your personal information shared with someone who is not on the study
49 team and was not supposed to see or know about your information. The study team plans to
50 protect your privacy – see the Confidentiality section above for details.
51
52

53 **Questionnaire**

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

1	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
2				
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4				
5	Methods: Participants, interventions, and outcomes			
6	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
7				
8				
9	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
10				
11				
12	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
13				
14				
15		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
16				
17				
18		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9,11
19				
20				
21		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
22	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
23				
24				
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26				
27	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
28				
29				
30	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
31				
32				
33	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
34				

Methods: Assignment of interventions (for controlled trials)

Allocation:

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39	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
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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

1	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
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4		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
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6				
7	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
8				
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
11				
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14	Ethics and dissemination			
15	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15,16
16				
17				
18	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
19				
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21	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
22				
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24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
25				
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27	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
28				
29	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
30				
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32	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
33				
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35	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
36				
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38	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
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1	31b	Authorship eligibility guidelines and any intended use of professional writers	16
2	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
3			
4			

Appendices

5				
6				
7	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
8				
9	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
10				
11				

*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.

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