INTERVAL: VARYING INTERVALS OF ART TO IMPROVE OUTCOMES IN HIV

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The INTERVAL Study: Varying Intervals of ART Dispensing to Improve Outcomes in HIV

Sponsored by:
USAID/PEPFAR

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ABBREVIATIONS AND ACRONYMS

ARV: antiretrovirals
ART: antiretroviral therapy
CAG: community ART group
CMC: clinical Management Committee
DMC: differentiated model of care
DSMB: data safety and monitoring board
CRF: case report form
EC: ethics committee
IRB: Institutional Review Board
MMS: Multi-month scripting/dispensing
PEPFAR: President's Emergency Plan for AIDS Relief
PID: Patient Identification Number
SOP: Standard Operating Procedure
TA: Technical Assistance
USAID: United States Agency for International Development

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Document Upload: Study Protocol and Statistical Analysis Plan

SCHEMA

Purpose:	To evaluate the effectiveness of two strategies for multi-month scripting/dispensing of antiretroviral therapy on retention and virologic suppression compared to standard of care
Design:	Unblinded cluster-randomized controlled trial
Study Population:	HIV-1-infected adults (18 and older)
Sample Size:	10 clusters in each of three arms representing ~8,200 patients
Intervention:	Arm 1: Standard of care scripting/dispensing Arm 2: Three-month scripting/dispensing Arm 3: Six-month scripting/dispensing
Study Duration:	Approximately 42 months total. Accrual is expected to require approximately six months, and enrolled participants will be followed for 36 months with the primary endpoint defined at 12 months and follow-up through 36 months

Primary Objectives

- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of three months is non-inferior to standard of care for the primary outcome of retention at 12 months
- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of six months is non-inferior to standard of care for the primary outcome of retention at 12 months
- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of six months is non-inferior to three months for the primary outcome of retention at 12 months

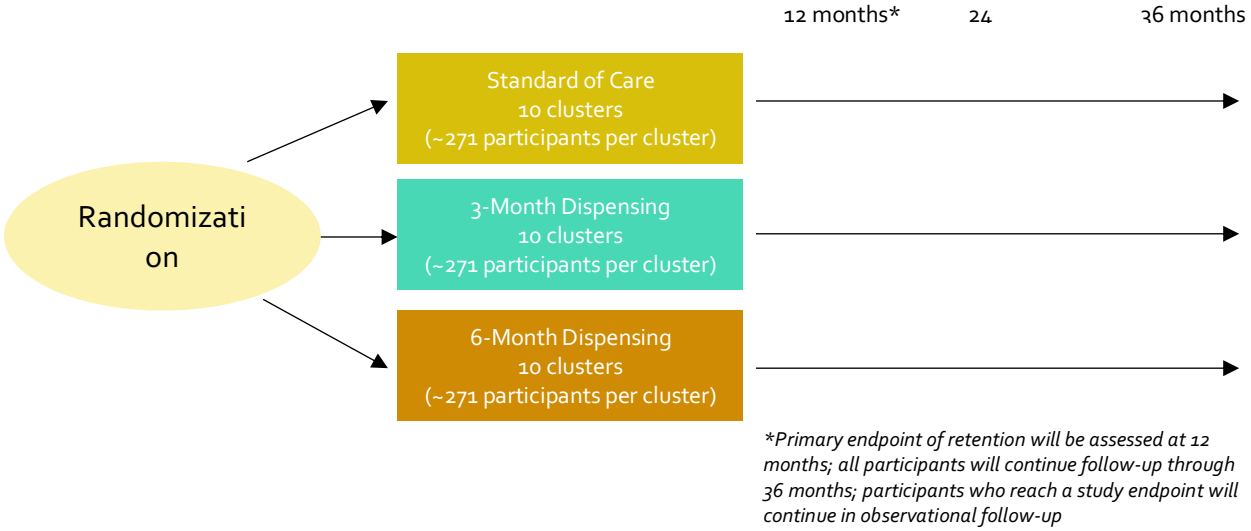
Secondary Objectives

- To determine whether scripting/dispensing of ART for intervals of three months is non-inferior to standard of care for the outcome of viral load <1,000 copies/mL at 12 months
- To determine whether scripting/dispensing of ART for intervals of six months is non-inferior to standard of care for the outcome of viral load <1,000 copies/mL at 12 months
- To determine whether scripting/dispensing of ART for intervals of six months is non-inferior to three months for the outcome of viral load <1,000 copies/mL at 12 months
- To evaluate the impact of scripting interval on retention and virologic suppression at 24 and 36 months
- To compare cost and cost-effectiveness of all three arms
- To determine whether three- and six-month scripting/dispensing is (all assessed at 12 months):
  - Feasible and acceptable for patients
  - Feasible and acceptable for providers
  - Feasible with regard to expanding supply chain and pharmacy storage
  - Non-inferior with regard to clinic resource allocation

- Safe in regard to impact on the drug compound after storage for six months (based on sampling of any unused drug at the end of the six-month period)

The INTERVAL Study: Varying Intervals of ART Dispensing to Improve Outcomes in HIV

Figure 1
OVERVIEW OF STUDY DESIGN



**Primary endpoint of retention will be assessed at 12 months; all participants will continue follow-up through 36 months; participants who reach a study endpoint will continue in observational follow-up*

1 STUDY POPULATION

This study will be conducted among approximately 8,200 HIV-infected individuals 18 years or older who are stable on antiretroviral therapy in 30 clusters who will be selected for the study according to the criteria outlined below. The following countries are planned to participate: Malawi and Zambia.

Sites will be selected based on size, ability to perform viral load determination as part of routine care, completeness of medical records, and ability to stock a six-month supply.

1.1 Inclusion Criteria

All of the criteria listed below must be met in order for an individual to be included in this study.

4.1.1 At least 18 years of age and willing and able to provide written informed consent for participation in this study

4.1.2 Confirmed HIV-1 infection based on country standard of care for testing

4.1.3 "Stable" on ART defined as
(1) On ART ≥ six months
(2) On a first-line ART regimen as defined by country specific guidelines
(3) No drug toxicity/tolerability issues within the prior six months
(4) No period of >one month without medication possession in the last six months
(5) No active opportunistic infection suspected (including TB) and not treated for an opportunistic infection in the last 30 days
(6) Undetectable viral load (as defined by country guidelines) within the last 6 months:
- Malawi: <1,000 copies/mL
- Zambia: <20 copies/mL

4.1.4 Not treated for other chronic health problems or comorbidities (e.g., high blood pressure, diabetes) at the clinic in which they receive their ART

4.1.5 Women will be included as long as they are not currently pregnant, not currently breastfeeding, and ≥6 months postpartum if they have recently delivered a baby

4.1.6 Planning to receive HIV care from the same facility for ≥1 year

1.2 Exclusion Criteria

Individuals will be excluded from the study if any of the following are identified during screening or any other time during the study:

4.2.1 Elevated viral load (as defined by country guidelines) of standard assay within the prior six months:
- Malawi: ≥1,000 copies/mL
- Zambia: ≥20 copies/mL

4.2.2 On alternative first-line or second-line regimen

4.2.4 >One month without medication possession in the last six months

4.2.5 ARV toxicity or tolerability issue within the prior six months

4.2.6 Suspected or diagnosed with an opportunistic infection (including tuberculosis) within the prior 30 days

4.2.7 Currently receiving treatment for a comorbidity (including hypertension or diabetes) at the facility in which they receive their ART

4.2.8 Pregnant or less than six months postpartum

4.2.9 Women who are breastfeeding

4.3.1 Unwilling or unable to provide informed consent

4.3.2 Previously enrolled in the study

4.3.3 Currently enrolled in a research study at the site that influences frequency of clinic visits and/or where they receive their medications

4.3.4 Currently participating in an ART support group, a community ART group (CAG), or a group where they receive ART at a location other than the clinic

4.3.5 Not planning to receive HIV care from the same facility for ≥1 year

2 INTRODUCTION

2.1 Background

The 2015 WHO Guidelines on when to start antiretroviral therapy recommend ART initiation regardless of CD4 count, with lifelong continuation to optimize individual health and prevent HIV transmission [1]. In order to realize the benefits of lifelong ART, high levels of adherence and retention will be needed. Barriers to adherence and retention have included long duration of wait times in ART clinics, cost of travel to clinics, and life events that result in interruptions in therapy. Requirements for monthly dispensing and/or systems that require multiple separate visits for refills and clinician evaluation can raise significant challenges for individuals living with HIV and result in treatment interruptions or complete disengagement from care [2]. Extension of interval refills has been employed in many settings, with supply provided up to every six months for stable patients in settings where resources have been available. This document will outline considerations for extending ART dispensing intervals. Given not all PEPFAR sites provide or have a mechanism for scripting either electronically or with paper-based methods, this document will refer to multi-month scripting/dispensing (MMS) to describe the process of supplying medications for an extended interval of time.

Potential benefits of multi-month dispensing/scripting include:

- Improved adherence to ART and retention in care through decreasing barriers such as time for clinic visits and cost of travel to clinics/dispensing sites; less risk of interruption due to unanticipated life events that result in missed clinical and/or pharmacy refill visits
- Reduced per-patient cost of providing ART, by reducing the number of clinic visits required

- Decongestion of clinics to allow for increased capacity to manage newly diagnosed patients, those with infectious complications, treatment failure, and other co-morbidities
- Decreased waiting time and improved efficiency at clinics allowing for improved quality of care and patient satisfaction

PEPFAR has adopted the goals of 90-90-90 from UNAIDS and the new guidelines of WHO on when to initiate ART. The goals of 90-90-90 are simple but ambitious – identify 90 percent of people living with HIV; link and initiate 90 percent of those identified on ART; and achieve viral suppression in 90 percent of those on ART, by 2020. This will result in 28 million people on treatment by 2020. With these goals, PEPFAR also sets out to reduce new infections by 75 percent and to attain zero discrimination and stigma for supported sites. PEPFAR funding changes for the upcoming year have been made to support a swift implementation of the new Test and Start guidelines. The goal is for implementation to occur within weeks to months, not years. The funding changes from the FY16 PEPFAR Technical Considerations are as follows. Countries that move to Test and Start are eligible for one-time commodities funds to immediately expand drug availability for longer follow-up intervals (Impact/Incentive Funds). The cost savings from adopting increased follow-up intervals and fewer laboratory tests should be used to dramatically expand treatment.

Requirements for frequent dispensing of ART (once every one to two months) places demands on the health system and can lead to suboptimal adherence and disengagement in care due to the time and cost of frequent visits to clinic. Keeping these considerations in mind, scaling up of HIV treatment must be accompanied by measures to allow stable patients to have an adequate supply of ART (at least three months) and should consider whether longer drug supply intervals are feasible (up to six months) and result in improved outcomes and/or lower costs. Attaining the benefits associated with 90-90-90 will require (I) support from the National AIDS Programs of multi-month dispensing, its incorporation in the national guidelines, and costing; (II) ARV forecasting and support for supply chain and pharmacy; (III) selection of appropriate patients for extended dispensing intervals and integration with current and planned differentiated models of care; (IV) support for implementation at site and community levels through mentorship and continuous training and support; and (V) monitoring and evaluation to confirm patients are adherent (ideally shown with viral suppression) and are retained in care.

I. **Support from the National AIDS program of the multi-month dispensing and its incorporation into the national guidelines including costing**
    a. Support the MoH to review, adopt, and adapt policies and guidelines to include multi-month dispensing, including costing for increased drug supply and strategies for the integration into both traditional clinic settings and within current and proposed differentiated models of care for ART.

II. **Preparedness and implementation for multi-month dispensing, including ARV forecasting and support for supply chain (including storage) and pharmacy**
    a. Preparation for multi-month dispensing will require support for forecasting the necessary ARV supplies needed to prevent stock-outs, assessment of current medication storage capacity, and support for increasing storage to accommodate dispensing needs (up to

three- to six-month supply). EQUIP will provide TA in these areas including an assessment of current pharmacy regulations and capacity for scripting (with consideration for use of an electronic national system such as a 'cloud', where feasible) and dispensing. Priority will be to support placing stable patients on a minimum three-month schedule and consideration of up to six-month ART supply in settings where this may be feasible. Countries interested in comparing provision of a three- versus six-month supply of ART may choose to participate in a multi-country demonstration project evaluating patient outcomes, cost, and impact on health system efficiencies.

III. Selection of individuals for multi-month dispensing and integration with current or planned differentiated models of care

a. As an initial step towards multi-month dispensing, defining 'stable' individuals for this care strategy will be required. EQUIP will provide support to define ideal scenarios and simple algorithms for identifying stable individuals on ART in whom extension of supply will be appropriate. For example, stable patients may be defined as taking ART for at least one year with either a suppressed viral load (in countries with immediate capacity to perform viral load testing) or adherence based on pill counts and appointment schedules (for those without immediate viral load capacity) and no other complicating health problems such as active infectious complication.

b. HIV care is moving towards differentiated models where many individuals may participate in community-based ART delivery programs (community ART groups, adherence clubs, etc.) and programs that may employ alternative strategies for drug delivery (community drop off/distribution points), and multi-month dispensing will need to be integrated into these programs. Integration of multi-month dispensing may include consideration of utilizing lay health workers, patients, or other non-clinician health cadres to pick up medications from pharmacy/clinic locations, and/or utilize alternative methods of drug storage and dispensing that can easily be accessed by the community. These strategies will depend on country-specific pharmacy and drug storage regulations and flexibility/adaptability of systems.

IV. Support for expansion/implementation of multi-month dispensing at site and community levels

a. Based on final plans for multi-month dispensing, mentoring will be needed at all levels of the health system. Clinicians will require training in identification of stable patients for multi-month dispensing and mentoring to utilize systems that are in place to enable these strategies (scripting versus use of decentralized pharmacy systems or drug pick up points). Clinicians and community care workers will need clear, ongoing mentorship to be in a position to educate and support patients and continue to optimize adherence and retention. With the change to viral load monitoring, care should be taken to ensure the patient's understanding of the benefits of maintaining an undetectable viral load, such as low transmittance, decreased opportunistic infections, increased CD4 count, and ultimately better health outcomes.

b. Pharmacists and related personnel will require mentoring to understand the variety of methods in which drug delivery may be employed in the health system and to ensure continuous quality improvement around drug storage and ARV forecasting.

V. Monitoring and evaluation of outcomes of adherence and retention in care and resource utilization with multi-month dispensing

In order to determine best practices around multi-month dispensing, programs will require monitoring and evaluation of systems (related to issues such as drug supply, adequacy of drug storage facilities, quality of pharmacy services, and resource utilization) and monitoring and evaluation of critical program outcomes such as viral suppression and retention in care. Data around improvements in these outcomes after switching to multi-month dispensing can be used to define best practices and to further scale programs within a given country and in other countries.

2.2 Prior Research on Multi-Month Scripting/Dispensing

There is limited rigorous data on multi-month scripting and dispensing from resource-limited settings. A review of the literature reveals no randomized studies of different dispensing intervals. An abstract from Zambia presented at CROI in February 2016 suggests that requirements for monthly dispensing and/or systems that require multiple separate visits for refills and clinician evaluation can raise significant challenges for individuals living with HIV and result in treatment interruptions or complete disengagement from care [2].

2.3 Rationale

Requirements for frequent dispensing of ART (once every one to two months) places demands on the health system and can lead to suboptimal adherence and disengagement in care due to the time and cost of frequent visits to clinic. Keeping these considerations in mind, scaling up of HIV treatment must be accompanied by measures to allow stable patients to have an adequate supply of ART (at least three months) and should consider whether longer drug supply intervals are feasible (up to six months) and result in improved outcomes. We propose a strategy trial of different intervals of ART dispensing with the goal of estimating any potential benefits of longer dispensing intervals with respect to retention, virologic suppression, and cost.

2.4 Hypotheses

Among adults with HIV infection who are stable in care:

- H1: Dispensing for three months will be non-inferior to SOC in regard to retention at 12 months
- H2: Dispensing for six months will be non-inferior to SOC in regard to retention at 12 months
- H3: Dispensing for six months will be non-inferior to three months in regard to retention at 12 months
- H4: Dispensing for three or six months will be non-inferior to SOC in regard to virologic suppression at 12 months
- H5: Dispensing for six months will be non-inferior to three months in regard to virologic suppression at 12 months
- H6: Dispensing for three or six months will be cost-effective compared to SOC

3 OBJECTIVES

Primary Objectives

- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of three months is non-inferior to standard of care for the primary outcome of retention at 12 months
- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of six months is non-inferior to standard of care for the primary outcome of retention at 12 months
- To determine, in patients stable on ART, whether scripting/dispensing of ART for intervals of six months is non-inferior to three months for the primary outcome of retention at 12 months

Secondary Objectives

- To determine whether scripting/dispensing of ART for intervals of three months is non-inferior to standard of care for the outcome of viral load <1000 copies/mL at 12 months
- To determine whether scripting/dispensing of ART for intervals of six months is non-inferior to standard of care for the outcome of viral load <1000 copies/mL at 12 months
- To determine whether scripting/dispensing of ART for intervals of six months is non-inferior to three months for the outcome of viral load <1000 copies/mL at 12 months
- To evaluate the impact of scripting interval on retention and virologic suppression at 24 and 36 months
- To compare cost and cost-effectiveness of all three arms
- To determine whether three- and six-month scripting/dispensing is (all assessed at 12 months):
    - Feasible and acceptable for patients
    - Feasible and acceptable for providers
    - Feasible with regard to expanding supply chain and pharmacy storage
    - Non-inferior with regard to clinic resource allocation
    - Safe in regard to impact on the drug compound after storage for six months (based on sampling of any unused drug at the end of the six-month period)

4 STUDY DESIGN

The study will be a cluster randomized trial comparing three different ART dispensing strategies. Clusters will be comprised of individual clinics in Malawi and Zambia.

Individuals will be screened at routine clinic visits and enrolled if they meet inclusion criteria (see below). Enrolled individuals will receive standard of care at their site with the exception of dispensing interval based on the assigned randomization. Outcomes will be assessed after 12 months but all patients will be followed for 36 months, with annual re-assessment of endpoints of retention and virologic suppression and evaluation of cost-effectiveness at those time points.

4.1 Recruitment, Screening, and Enrollment Process

Recruitment methods for this study may vary across sites but are expected to rely on active identification and referral of stable patients, as defined above, by clinic staff. Clinics will be randomized to a study arm, and individuals will initiate the study drug dispensing interval to which the clinic has been randomly assigned.

Each study clinic will be asked to provide a list of potential study participants, based on time on ART. Records will then be reviewed to screen out those who do not meet inclusion criteria, based on available information. Upon identification of a potentially-eligible individual, study staff will provide information about the study to the patient. Individuals who express interest in learning more about the study will be provided additional information as part of the study informed consent process. The process will include detailed review of the study informed consent form, time to address any questions or concerns, and an assessment of the individual's understanding before proceeding to an informed consent decision. The process will be fully documented, and only individuals who are able to demonstrate understanding will be asked to provide written informed consent for study screening and enrollment.

Each country will require IRB approval from their local authority, and written informed consent will be required. Additionally, each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed, roles and responsibilities for performing the required procedures, roles and responsibilities for assessing and confirming eligibility, and procedures for documenting the process. These will be described in detail in IRB applications. Participants will be informed of the assigned drug-dispensing interval based on the facility randomization assignment — standard of care, three, or six months — and the appropriate quantity of medications will be prescribed/dispensed on the day of enrollment.

When informed consent is obtained, a participant identification number (PID) will be assigned to the individual.

4.2 Co-Enrollment Considerations and Differentiated Models

After enrollment in the INTERVAL study, co-enrollment in other studies will not be allowed given the likelihood that this will interfere with the primary study endpoint of retention.

Differentiated models of care (DMCs) will be included as follows: if a facility utilizes differentiated models such as adherence clubs, CAGS, or drop off points, these facilities will be included in the study, though patients participating in DMCs will be excluded from the study.

4.3 Randomization

Randomization will be conducted at the level of a hospital and surrounding clinics. We will randomize 30 clusters evenly to one of three arms: standard of care, three-month dispensing, and six-month dispensing. All patients enrolled at the site will follow the treatment assignment for the cluster in which they are randomized. Clusters will be matched in groups of three on available information that might predict outcomes, including country, type of facility (hospital/health centre), clinic size, number retained on ART, location (rural/urban), etc. We will then randomly allocate one cluster in each group of three matched clinics to each treatment arm. This will help minimize residual confounding that can result in cluster randomized trials.

4.3.1 Description of Study Arms

A randomization tool in Microsoft Excel will be used to randomly assign clusters to study arms. Clusters will be assigned to one of three arms:

1. Standard of care arm: The standard of care arm will allow dispensing based on usual practice at the clinic. Standard of care is anticipated to have variability in how ART is dispensed, although the approach should be consistent with applicable country guidelines at the time of study. For example, if country guidelines recommend provision of two months of ART to stable patients, we expect most patients will receive two months; however, providers may choose to deviate from this standard for some patients, and the study will not influence these patterns. We recognize that in countries with three-month dispensing as the norm, standard of care may be similar to the three-month dispensing arm; however, we do anticipate an increased degree of variability in prescribing practices at these sites, either based on provider or patient preference.

2. Three month dispensing arm: Providers at facilities randomized to three-month dispensing will be expected to provide all enrolled patients with a 90-day supply of ART. All other aspects of care will be as standard of care for the enrolling clinic, though routine clinic visits will occur every 90 days instead of the standard of care interval. Information about ideal storage conditions for ART will be provided by the clinic. In a subset of patients, unused ART will be returned to the site and submitted to the study team for analysis to evaluate whether typical storage conditions have any negative impact on active drug compound.

3. Six month dispensing arm: Providers at facilities randomized to 6-month dispensing will be expected to provide all enrolled patients with a 180-day supply of ART. All other aspects of care will be as standard of care for the enrolling clinic, though routine clinic visits will occur every 180 days instead of the standard of care interval. Information about ideal storage conditions for ART will be provided by the clinic. In a subset of patients, unused ART will be returned to the site and submitted to the study team for analysis to evaluate whether typical storage conditions have any negative impact on active drug compound.

4.4 Informed Consent

Oral informed consent will be obtained prior to screening procedures. The oral consent process will include a brief overview of the study, information about the screening procedures, alternatives to participating in the screening, and a brief assessment of the patient's understanding of the consent. If a patient does not have a viral load recorded within the prior six months but has passed all other eligibility criteria, then written informed consent will be obtained before a viral load test is performed.

Written informed consent will be obtained prior to enrollment and any study-specific procedures are performed (including blood draw for a viral load test during the screening procedures). The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the randomized nature of the study and the differences that participants may experience as part of the study relative to current local standards of care.

4.5 Participant Retention

Because retention in care is a primary outcome for the study, once an individual is enrolled, there will be no additional efforts applied towards retention with the exception of standard of care counseling and other retention support offered by sites. Study interactions with participants will be minimized through use of existing medical records to track patient outcomes. We will obtain informed consent to contact people after completion of the study to perform qualitative interviews and surveys of acceptability, cost, and quality of life measures.

4.6 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, individuals may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Site investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs

For any participant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations. In the event that the circumstances that led to a participant's withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the study investigators to discuss options for resumption of follow-up.

5 STUDY VISITS AND PROCEDURES

An overview of the schedule of study visits and evaluations is provided in Table 3 below. Presented in this section is additional information on visit-specific study procedures.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information and reviewing elements of informed consent.

Table 3: Schedule of Evaluations

Evaluation	Entry	12 months	24 months	36 months
Administrative/Regulatory • Informed Consent • Complete final eligibility determination and confirmation*	X			
Clinical History/Socio-demographic data • Date HIV diagnosis • Socio-demographic data • ART start date • Medications at entry (ART, CPT, IPT) • ART dispensing interval at time of entry • CD4 at ART initiation/CD4 if documented within 12 months prior to entry • VL at entry	X			
Medical Record Review for Endpoint^ • Retention in care* • Viral load • ART regimen changes • Medication review (CPT, IPT) • Current dispensing interval (*if changed, date of change and reason for change documented*) • Interval lab tests recorded, if any (CD4) • OIs if recorded		X	X	X
Patient Health Passport Review for Endpoint^ • Number and type of interval clinic visits (unscheduled) • General health assessment		X	X	X
Time and Motion Assessment • Patient wait times	X	X	X	X
Cost Assessment	X			
Clinic Resource Allocation Assessment	X	X	X	X
Qualitative in-depth interview		X		X
Qualitative in-depth interview and survey with providers		X		X

^Individuals who meet an endpoint will be followed for the remainder of the study in observational follow-up;
*Default defined as out of ART >6o days

5.1 Screening Visit

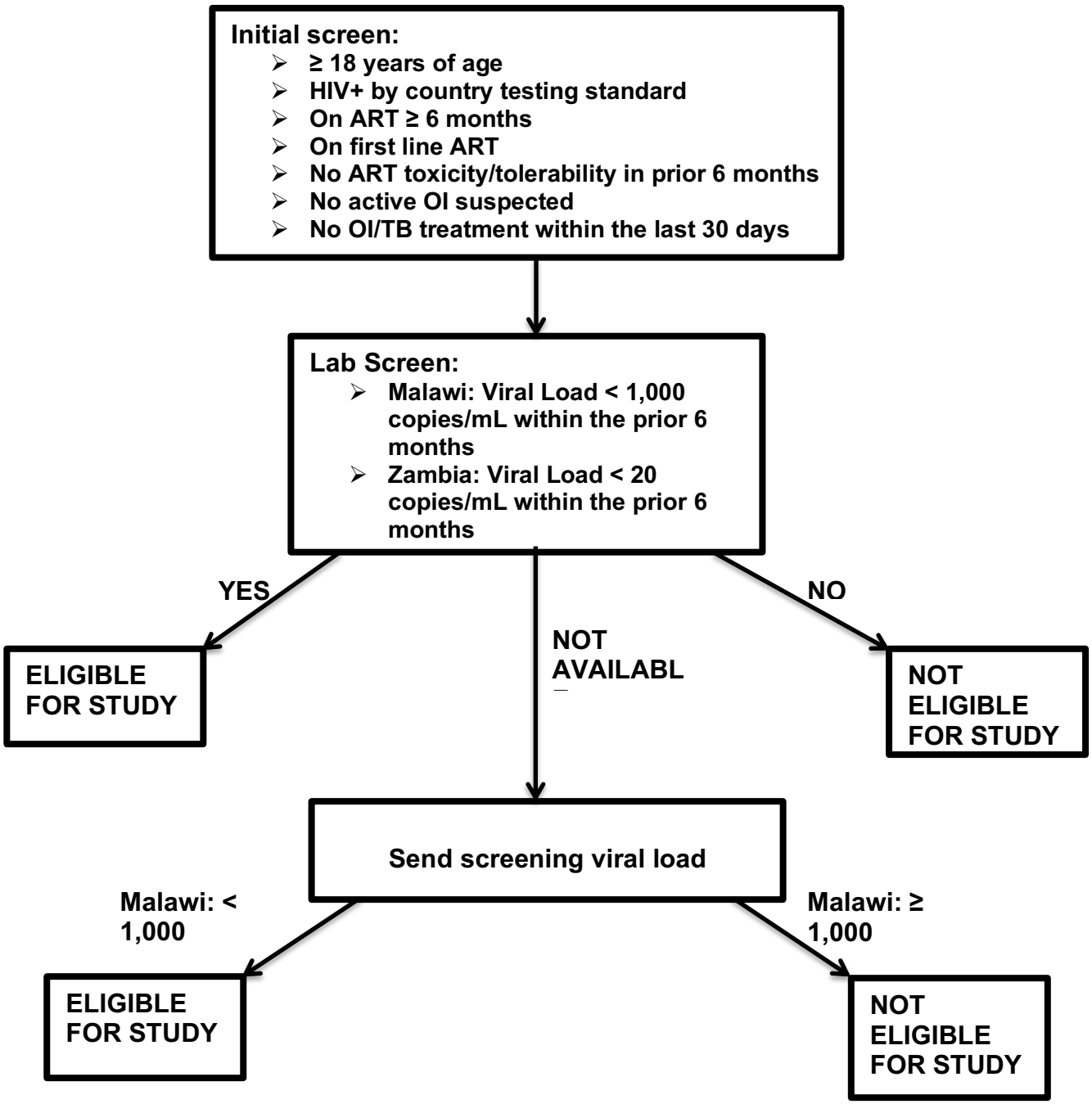
An overview of the screening visit procedures is provided in Table 1 below. Initial screening will include review of participant clinical data and will be performed at the time of routine ART visits to clinic. If inclusion criteria are met with the exception of viral load (due to missing viral load information), a viral load test will be performed if not documented within the last six months. Viral loads should not be drawn until participants have met other inclusion criteria (Figure 2: Screening Algorithm). If viral load is savailable, the screening and entry visit procedures can be combined into the same visit. If no viral load is available, the viral load is performed and entry will occur at the time the participant comes back at the next routine appointment. Given the next routine appointment could be up to three months later, the screening criteria should be reviewed again before the entry visit procedures are performed.

Table 1: Screening Visit

Screening Visit Procedures	
Administrative and Regulatory	• Obtain informed consent from participant before screening
Screening Data from Medical Record	• Review medical chart for: ➢ ≥ 18 years of age ➢ Confirmation of HIV+ status^ ➢ Confirmation of ART for ≥six months ➢ No period of >one month without medication possession in the last six months ➢ ART regimen is standard first-line regimen ➢ No suspected or confirmed infectious complication (including tuberculosis) within the last 30 days (i.e. must be off treatment for other condition for >30 days at time of entry) ➢ Not currently pregnant or within six months of delivery
Laboratory	• Review chart for most recent viral load (viral load must be <1,000 copies/mL within six months of screening for Malawi and must be <20 copies/mL within six months of screening for Zambia) • If no viral load available, ask clinic to draw blood sample and send for viral load test

^based on recording of HIV status in medical record

Figure 2: Screening Algorithm
(Note: If screening viral load needs to be sent, participant follows up for study entry at next routine ART visit. At that visit, screening criteria will be re-reviewed and if still eligible and VL<1000, copies, study staff will proceed with entry)



5.2 Entry Visit

An overview of the entry visit procedures is provided in Table 2 below. All entry visit procedures are expected to be performed on the day of enrollment; procedures that may provide information relevant to eligibility for the study (e.g. viral load), should be performed first, prior to final eligibility determination.

Additional requirements for sequencing of procedures at the entry visit are as follows:

- Final eligibility determination and confirmation and provision of written informed consent must precede enrollment
- Enrollment and entry visit procedures must precede dispensing of ART

Collection of clinical history information is required at the entry visit. All history information will be obtained based on self-report and available medical records. Relevant dates will be recorded for all conditions and medications.

Table 2: Entry Visit

Entry Visit Procedures (Day 0)	
Administrative and Regulatory	• Complete signed informed consent* • Complete final eligibility determination and confirmation*
Clinical/Medical Record Review **Surveys**	• HIV history, HIV-related medications, date of ART initiation, prior adherence/VL data • Socio-demographic data including age, gender, highest level of education, distance to travel to clinic, household composition (number of adults and children in household), employment status, disclosure status, marital status • Collection of patient cost data: travel time and costs to clinic, opportunity cost of time spent on medication pickup visits
Dispensing	• After enrollment, site clinician dispenses ART per cluster randomized assignment

*Performed prior to entry visit procedures

5.3 Annual Viral Load Visit (12 months, 24 months, 36 months)

There will be no contact with study participants during the period of follow-up. However, when participants are due for routine, annual viral load assessments, study staff will help ensure each site has capacity to collect these samples and will support systems that help to provide results back to sites. Viral loads will only be performed on individuals who return for visits, and no tracing will be performed by the study for the purpose of obtaining viral load. Viral loads will be considered within the window for the annual visit if they are performed in a window of +/- 60 days.

5.4 Definition of Study Endpoints

Endpoints will be determined by chart review after the primary endpoint is reached (12 months) and will be re-assessed after the 24-month endpoint and again after the 36-month endpoint. Endpoint data collection will include:

(1) Retention in care on strategy (not lost to follow-up and not changed off dispensing interval; lost to follow up will be defined by being out of ART for >60 contiguous days) (primary)
(2) Suppressed viral load of <1,000 copies done as part of annual viral load or performed at any other time during the follow-up, if ordered by clinician due to clinical concern (secondary)

The following will be considered not retained unless otherwise noted:

- Retained in care but with transitioned off assigned study arm for any reason (patient preference, provider preference, development of ART toxicity requiring switch and closer monitoring, OI, other complication)
- Transferred to another clinic (if a documented transfer, will be considered retained and analyzed as such at the next assessment point (12, 24, or 36 months)
- Death

Observational Follow-Up

All participants with loss to follow-up will be traced by existing clinic protocols (if present). If they are located and return to clinical care, medical records will be reviewed up to the 36-month time point to determine outcomes after loss to follow-up. Additionally, those with virologic failure will reviewed at subsequent time points for additional outcomes. Chart review will be performed at subsequent time points to determine outcomes such as:

- retained and suppressed (and dispensing interval)
- retained but not suppressed (and dispensing interval)
- retained but dispensing interval changed for any reason
- lost to follow up again (defaulted care defined by >60 days without ART)
- transferred
- died

Health Passport Review (Malawi only)

In a subset of participants (n=1,500), we will perform a review of participants' health passports, a record of patient clinic visits, general health information, and medications that is possessed by patients in Malawi, after the 12-, 24-, and 36-month endpoint has been completed. Informed consent will be obtained at entry for permission to review participants' health passports during their endpoint ART clinic visits. Study staff will scan the health passports and store the records in a secure database. Physicians who are familiar with Malawian health records will review the health passports to collect patient data on interim clinic visits, such as reason for visit/services received (sick, family planning, non-communicable disease treatment), frequency of visits, and location of clinic services.

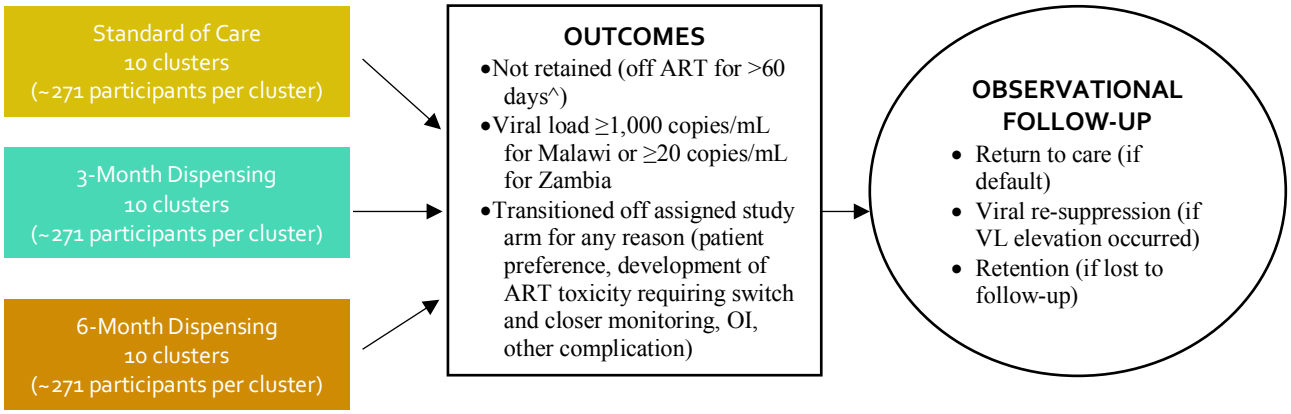
5.5 Post-Intervention Visit

In a subset of participants (~240), we will perform a post intervention study visit after the 12-month endpoint is completed and also after the 36-month endpoint is completed. Informed consent will be obtained at entry for permission to contact participants after the study is over. Qualitative interviews will be performed with a subset of participants with the goal to include those that were retained in care as well as participants who reached a study endpoint. Questions will focus on patient experience with assigned dispensing interval, including challenges/barriers and facilitators towards adherence and retention. Focused questions around endpoints (if default, reasons; if virologic failure, reasons including adherence) will also be addressed in the post-intervention visit.

5.6 Time and Motion Assessment

In a random sample of up to 100 patients per clinic, we will perform a time and motion assessment at study commencement and again at each study endpoint. Participants already enrolled in the study will be excluded from the time and motion assessment. Wait times will be measured by research staff, and patients will be surveyed about clinic services received during their visit. Assessments will occur on randomly selected ART clinic days.

Figure 3: Summary of Plan for Follow-up



^Participants who are lost to follow-up will be traced by routine clinic based protocols; individuals who return will be continued on study in observational follow-up

5.7 Virologic Failure

In the event that an elevated viral load returns (≥1,000 copies/mL for Malawi or ≥20 copies/mL for Zambia), clinics will be expected to manage the participant as per the country guidelines with adherence counseling. Frequency of ART dispensing will be determined based on guidelines and clinician assessment. No additional study visits will

be performed at the time of virologic failure. Virologic failure will be captured via medical record review. These individuals will remain in observational follow-up.

Viral load will be collected based on standard of care for the site as dictated by each country program and reported based on the threshold used for clinical management by the country program. Suppression will be defined by as <1,000 copies/mL.

5.8 Drug Supply

The standard of care first line regimen will be provided by the sites. EQUIP will support supply chain and medication storage as needed to ensure that all participants are able to receive the appropriate extended interval refill and that study ART needs do not negatively impact supply chain needs at non-study sites or for non-study patients.

In the event lost or stolen medication is reported by a participant, the clinic will proceed with standard of care procedures for re-dispensing of medications as defined by the country's guidelines. Participants who report lost or stolen medication will remain in their assigned study arm and ART dispensing interval unless termination from the study has been deemed necessary per guidelines in section 4.6.

6 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections below describe safety-related roles, responsibilities, and procedures.

6.1 Safety-Related Roles and Responsibilities

6.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

6.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Protocol Chair and Vice Chair, selected Protocol Investigators, Statisticians, and Data Managers. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events.

6.1.3 Data and Safety Monitoring Board (DSMB)

An independent DSMB will be assembled and will have at least three representatives from settings in which the study is being performed, one of whom will be a biostatistician. The primary purpose of the DSMB will be to perform one interim analysis after half of the primary study outcomes have been reached to determine whether the study needs to be stopped early for a positive result or whether issues such as slow enrollment or loss to follow-up could impact study goals.

6.2 Management of Participants Who Develop Tuberculosis or Another Opportunistic Infection

Participants who develop TB or other opportunistic infections may require more frequent follow-up than required by their dispensing interval. Frequency of ART dispensing will be determined based on guidelines and clinician assessment. No additional study visits will be performed at the time of these clinical complications or changes in dispensing interval. These events will be captured via medical record review. These individuals will remain in observational follow-up.

6.3 Management of Women Who Become Pregnant During Study

Women who become pregnant during the study may require more frequent clinical visits than required by their dispensing interval. Frequency of ART dispensing will be determined based on guidelines for ART in pregnancy and clinician assessment. No additional study visits will be performed at the time of pregnancy or change in dispensing interval. These events will be captured via medical record review. These individuals will remain in observational follow-up.

7 STATISTICAL METHODS

7.1 General Design Issues

The study will be a three-arm cluster randomized trial. Accordingly, the analysis and sample size will need to account for statistical clustering within groups allocated to interventions and control arms. In addition, we will conduct one interim analysis when the data for 50 percent of the participants are recruited and have reached a primary outcome at one year of follow up. Because we may not see large differences between the three-month dispensing and the six-month dispensing arms, we have powered the trial as a cluster randomized non-inferiority trial. This was done to ensure we had adequate sample size to draw conclusions even if no major differences exist but also to be able to detect differences between each intervention arm and standard of care.

7.2 Outcome Measures

7.2.1 Statistical Analysis for Primary Outcome Measures

Our primary outcome is retention in care at one year and is the basis for our sample size estimates and our primary analysis. Follow up will be passive by record review and will not involve any patient interaction with study staff as our goal is to measure retention under routine conditions.
Documented transfers will be considered retained at the next immediate time point of endpoint assessment and then will be censored. Deaths will be considered not retained.

Our analysis will begin with descriptive measures about the study population, stratified by treatment arm and by clinic and presented as medians and interquartile ranges for continuous measures and proportions for categorical variables. These measures will be used to look for large variations by clinic and for imbalances between study arms.

Our primary analysis will use a log linear generalized estimating equation to estimate the risk ratios and associated 95% confidence interval for the effect of each intervention arm compared to standard of care. We will specify clinic level clustering to account for the study design and estimate robust standard errors using an unstructured correlation matrix. Should we identify any baseline imbalances between study arms, we will adjust for these in our multivariable model and report adjusted risk ratios and corresponding 95% confidence intervals.

7.2.2 Statistical Analysis for Secondary Outcome Measures

Our study has not been powered to specifically look at secondary endpoints (described above), however we should have enough power to detect differences in our secondary endpoints if they exist. Our analytic methods for secondary outcomes will be identical to those for primary outcomes described above.

For other secondary outcomes, analysis is defined below individually for each:
To determine whether six-month scripting/dispensing is (all assessed at 12 months):

(1) Feasible and acceptable for patients: In a subset of participants in all arms, qualitative methods (semi-structured in-depth interviews) will be used to assess feasibility and acceptability of scripting/dispensing interval; impact on quality of life, health, adherence, ability to remain in care; challenges with storage of medications; and self-perceived benefits or harms of different scripting/dispensing intervals (with particular focus on whether there is difficulty with storage of medications, risk of theft, or pressure to exchange medications for money or food).
(2) Feasible and acceptable for providers: In a subset of providers in all arms, qualitative methods (semi-structured in-depth interviews) will be used to assess feasibility and acceptability of different scripting/dispensing intervals, including impact on clinic efficiency, systems of care around HIV, and patient outcomes.
(3) Feasible with regard to expanding supply chain and pharmacy storage: We will describe infrastructure in place at each of the clusters performing six-month scripting/dispensing and use study site surveys to understand challenges faced with forecasting, supply chain, and storage of medications.

(4) Safe in regard to impact on the drug compound after storage for six months (based on sampling of any unused drug at the end of the six-month period): Providers at facilities randomized to six-month dispensing will be expected to give a 180-day supply to all participants in the study. Information about ideal storage conditions for ART will be provided by the clinic. In a subset of patients, unused ART will be returned to the site and submitted to the study team for analysis to evaluate whether typical storage conditions have any negative impact on active drug compound.

8 COST AND COST-EFFECTIVENESS METHODS

It is expected that multi-month dispensing will reduce both facility and patient costs of treatment and that it will be cost-effective compared to standard of care. For facilities, fewer clinic visits by patients should save the time of providers and support staff. For patients, fewer clinic visits are expected to reduce the costs of travel and to save time. The study will estimate differences in both provider and patient costs. Cost-effectiveness will be estimated as the average cost per successful outcome (patient retained at 12 months). We will also collect data on proxy measures of resource allocation within the clinic, to determine whether multi-month dispensing affects overall access to care.

8.1 Costs to Provider

Costs will be measured from the provider perspective. We will use micro-costing methods developed and published by the investigators [3-5] to estimate the cost of providing ART to study patients in all three arms. We will first create an inventory of all the resources used to achieve the observed study outcomes from study enrollment to the specified endpoint (e.g. 12 months). Resources to be captured will include:

- ARV medications (medication names and quantities dispensed)
- Non-ARV medications that are prescribed in the course of HIV care (medication names and quantities dispensed)
- Laboratory tests (number and type)
- Outpatient clinic visits (number and type/purpose)
- Other services provided (e.g. counseling interactions, x-rays, etc.)
- Inpatient care if recorded in study clinic records (number of days admitted)
- Fixed costs of patient care (building space, equipment, management staff)
- Depreciated investment costs of establishing capacity for multi-month dispensing (e.g. drug storage capacity at the sites and clinic staff training).

For each study patient, the quantity (number of units) of resources used will be extracted from routinely maintained medical records, which will include registers and logbooks kept at facilities, individual patient files (paper and/or electronic), and off-site sources of data, such as a centralized laboratory or medical record database. Unit costs of resources, which are not human subjects data, will be obtained from external suppliers and the site's finance and procurement records and multiplied by the resource usage data to provide an average cost per study patient in each study arm. Costs will be

reported as means (standard deviations) and medians (IQRs) in USD, using the exchange rate prevailing during the follow up period.

8.2 Cost-Effectiveness

Using the average cost per patient as described above, we will then estimate the cost per outcome achieved in each arm. The main measure of effectiveness for the cost-effectiveness analysis will be the primary study outcome of retention in care at 12 months. We will compare average cost/patient retained in care across the three study arms, initially at 12 months and then again at 36 months. To provide information for HIV program budgets, we will also estimate the annual cost of providing ART under the three strategies being evaluated, independent of outcomes.

8.3 Patient Costs

Costs to patients for obtaining ART will be estimated on a per-visit basis. At study enrollment, patients will be asked about costs incurred per clinic visit for transport, food and/or accommodation during the visit, and wages lost and other time costs during the visit. For each patient, the number of clinic visits made per 12-month period for any HIV-related reason will then be multiplied by the cost per visit. Finally, we will estimate and compare the average cost per patient of obtaining care in each study arm.

8.4 Clinic Resource Allocation

We will use two proxy measures to assess whether multi-month dispensing affects access to care, by releasing clinic resources for other purposes. First, we will estimate average waiting time (minutes/patient from arrival at the clinic to seeing a clinician) among patients seeking HIV care at the study clinics before the start of the intervention and after 12 months of implementation. Data will be collected anonymously by an observer stationed at each clinic, who will record the waiting times for a sequential sample of patients over a several-day period. Second, we will use aggregate, clinic-level data (e.g. DHIS) to ascertain whether the quantity or mix of services provided changes between the last month before Year 1 and the first month of Year 2. None of the data collected for the clinic resource allocation analysis will be human subject data.

8.5 Sample Size and Accrual

8.5.1 Sample Size

Our sample size was estimated for three groups for a cluster randomized non-inferiority trial. We have 30 clusters available for randomization, and therefore, estimated our sample size assuming a fixed number of clusters (k) and an equal number of clusters per arm. We also assumed an equal number of participants per cluster. We estimated that about 5% of participants would fail to be retained in care in the intervention arms, and would accept up to 7.5% failure as non-inferiority. Assuming an alpha of 0.05 and power of 90% and an intracluster correlation coefficient of 0.004, we would need to enroll 271 participants per cluster for a total of 2,710 participants per arm and 8,130 total participants in the entire study. Because our primary outcome is retention, we will make no adjustment for loss to follow up. We will also increase our sample size to 8,200 as we will have one interim look at the data when 50% of the data are accrued.

Sample sizes of 2,710 in each arm will be obtained by sampling 10 clusters with 271 participants each in group to achieve 90% power to detect a non-inferiority margin difference between the group proportions of 0.025. We assume
the proportion achieving our primary outcome in the control arm will be 0.05 and will consider 0.075 to be non-inferior in either of the other two groups (six-month or three-month dispensing). The test statistic used is the one-sided Z test (unpooled). The significance level of the test is 0.05.

8.5.2 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones and quality of study conduct.

The team will closely monitor participant accrual based on reports that will be generated at least monthly. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. For any site that is delayed in completing the study activation process or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will similarly review key indicators of the quality of study conduct (e.g. data quality, and data and specimen completeness) based on reports and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation, particularly around completion of medical records which will be necessary to determine study endpoints.

8.5.3 Monitoring by the DSMB

The first analysis will be performed when 50% of the patients have completed 12 months. The DSMB will also be asked to look at whether the 30 clusters are adequately balanced and will provide advice regarding whether any adjustments are required to achieve balance (expand sites or replace sites). The study will be stopped early only if we find a difference between three- versus six-month dispensing with a $p<0.01$.

Operational futility may be considered if the observed accrual patterns are exceedingly different than planned, and the protocol team has had a chance to address the shortcomings of accrual.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Management Responsibilities

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including CRFs and supporting source data. Depending on capacity and infrastructure of sites/regions, data will either be collected by hand and entered into a database or collected electronically with data uploaded to a database.

All data must be transferred to the central database within timeframes specified in the forms instructions; queries must also be resolved in a timely manner.

10 SITE MONITORING

Site monitors under contract to EQUIP will visit study sites to inspect study facilities and review participant study records including consent forms and CRFs, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Site investigators will make study facilities and documents available for inspection by the monitors.

11 HUMAN SUBJECTS PROTECTIONS

11.1 Institutional Review Board/Ethics Committee Review and Approval including Informed Consent

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed, and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the EQUIP Protocol Team.

Written informed consent will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the randomized nature of the study and the differences that participants may experience as part of the study relative to current local standards of care.

11.2 Potential Benefits

There may be no direct benefit to participants who take part in this study, though participants who are placed in study arms randomly selected to receive a larger ART supply may benefit from reduced visits to their ART clinic. However, information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to optimized treatment guidelines for HIV-infected pregnant individuals.

11.3 Potential Risks

Most study procedures are routine clinical care associated with minimal to no risk in participants. Blood collection for viral load may cause pain, bruising, swelling, and (rarely) infection at the site where the needle is inserted. Participation in surveys and interviews may cause psychological stress or discomfort. Participants may decline to answer any questions that make them uncomfortable. Participants may also experience some added difficulties with storing and transporting their ART supply, as the study may require some participants to receive a larger ART supply than the standard of care. The increased ART supply may also make it more difficult for participants to keep their HIV status private if they have not disclosed their status to people in their home.

Study participants who are enrolled in the three- or six-month dispensing arms may also experience some divergences in the timing of their clinic appointments. For example, participants who are enrolled in a longer dispensing arm may be required to return to clinic more frequently for other medical reasons (e.g., birth control injections, postpartum and infant care for non-breastfeeding women, other medical care).

11.4 Reimbursement/Compensation

Participants will not be compensated for study participation. Participants will receive refreshments for their time during the screening and entry visit procedures. Participants who are randomly selected to participate in a post-intervention interview will receive a reimbursement for their transportation costs to/from the clinic.

11.5 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password-protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

11.6 Management of New Information Pertinent to Study Participation

Study staff will provide participants with any new information learned over the course of the study that may affect their willingness to remain in follow-up.

11.7 Post-Trial Access to Multi-Month Scripting/Dispensing

After completion of the study, follow-up participants will be transitioned to country standard of care for stable patients. We anticipate that data from the study will be utilized by countries to support multi-month dispensing at three-month intervals or longer.

12 ADMINISTRATIVE PROCEDURES

12.1 Regulatory Oversight

This study is sponsored by USAID/PEPFAR. EQUIP staff will perform monitoring visits. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable regulatory requirements.

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRBs/ECs, and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to EQUIP Protocol Team and leadership group. An EQUIP representative will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the EQUIP key personnel, and sites will receive an Initial Registration Notification from EQUIP that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the EQUIP Protocol Team. EQUIP key personnel will review the submitted protocol registration packet to ensure that all the required documents have been received.

12.2 Study Implementation

Study implementation at each site will also be guided site-specific SOPs. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

12.3 Protocol Deviation Reporting

All protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported to the Protocol Team as soon as possible.

13 PUBLICATIONS

All presentations and publications of data collected in this study are governed by EQUIP and USAID/PEPFAR policies.

14 REFERENCES

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