RETAIN6 PROPOSAL NARRATIVE

Problem statement

With the advent of rapid, same-day, and community-based ART initiation, the challenge of achieving optimal outcomes in HIV treatment has shifted even more fully onto retention after a patient has started ART. Consistently across both time and geography, the highest risk for loss from care is a patient's first six months after ART initiation. Dubbed the "early retention" period[1], this interval accounts for roughly three quarters of all first-year attrition from HIV programs in sub-Saharan Africa[2]. The most recent PEPFAR data from Zambia indicate that roughly half of patients started on ART experience treatment interruptions in their first six months[3]; across PEPFAR countries, patients in their first three months on ART are 2-4 times more likely to interrupt treatment than are those who've made it beyond 3 months[4]. In South Africa, 26% of patients were lost to follow up by 6 months after initiation in a recent trial of a case management intervention[5]. In a post-UTT observational cohort in Zimbabwe, of the 29% of patients lost from an observational cohort in the first 12 months after initiation, 88% were lost in the first six months and 77% in the first three months[6].

As we noted in a recent paper[7], there are likely to be several reasons for this, including both patient characteristics and service delivery characteristics. With regard to patient characteristics, after the WHO began recommending universal treatment access in 2016, the median CD4 count of new ART initiates rose substantially, reflecting the much higher proportion of asymptomatic, "healthy" patients than in the past[6], despite a fairly consistent minority of a quarter to a third continuing to present with very low CD4 counts[8,9]. The proportion of patients who are re-initiating ART after previously interrupting care is also climbing. A recent modeling exercise estimated that by 2020, fully 58% of those who test positive for HIV will already be aware of their positive status[10] and thus may have declined an earlier opportunity to start or remain on treatment. In Botswana in 2018, some 30% of patients presenting with advanced HIV disease were previous defaulters[11]. Individuals who know their HIV+ status but are not on ART likely face multiple barriers to starting treatment; those who both know their status and have already started and stopped ART at least once (re-initiators) may find remaining in care even harder.

Service delivery has also transformed in recent years for patients at many points in the cascade. The introduction of rapid and same-day ART initiation has shifted some attrition from before to after starting ART[12]. While it offers many advantages, same-day initiation, which our nearly-completed SPRINT study observed at very high rates in Malawi and Zambia and which is becoming common in South Africa, has the effect of designating patients as "initiated" regardless of whether they both are able and choose to remain in care after being dispensed their first supply of ARVs. At the same time, existing differentiated service delivery (DSD) models for ART offer much greater convenience to patients who meet the criteria for being "established" (previously "stable") on ART. These criteria nearly always include at least six, if not twelve, months' experience on ART, however[13], as illustrated in Figure 1. Current DSD models thus do little for those in the first six months after initiation. The advent of COVID-19-related restrictions and behavior changes seems likely to have made early retention even worse, though data are scarce.

Figure 1. Number of months on ART required prior to DSD model eligibility as of June 2021

Source: https://www.differentiatedservicedelivery.org/Portals/0/adam/Content/jcdklT8RzEqirRdlckAjbQ/File/1-Time%20to%20DSD%20Eligibility%20June2021%20WEB.pdf

Despite these large changes in population and service delivery, the model of care offered to most newly-initiating and re-initiating patients has barely evolved from its original outlines. Newly released 2021 WHO guidelines continue to recommend at least 6 months on ART as a prerequisite for eligibility for DSD models[14]. In the first six months after starting ART, most patients must still make multiple clinic visits that include clinical consultations with providers, and most can receive only 1-2 month supplies of medications at a time, regardless of patients' clinical condition or prior experience with ART. This model of care no longer meets the needs of many patients, leading us to the conclusion that "reconsideration of how to deliver ART during the first six months is warranted and overdue"[7].

Project overview

In the paper mentioned above, we presented a set of research questions to generate the information needed to optimize HIV treatment during a patient's first six months. These questions vary in the magnitude and duration of the work that will be needed to answer them. As a start, we would like to generate evidence to help answer the following questions:

1. Is a routine clinical consultation required between ART initiation and month 6, and if so, should it be mandatory for all or only for selected patients with conditions requiring it or who request it; exactly what procedures, tests, or other activities should it entail; what clinical cadre should provide it; and where and when should it take place? (Question 1 in the paper cited above[7])
2. What are the main reasons for unscheduled visits in this period; if data allow, what proportion of patients should have received additional services during their first 6 months but did not, based on findings at the routine 6-month visit; and, if data allow, what are the main reasons for missed visits in this period? (Question 3)
3. How much and what kind of non-clinical interaction (e.g. social support, HIV education, treatment literacy) with professional and/or lay healthcare providers, including counselors, is optimal between ART initiation and a patient becoming eligible for an existing, established-patient model of care? (Question 5)
4. Are there specific additional services or approaches that would help patients establish behaviors and long-term habits in support of ART adherence? (Question 7)
5. Is a system that offers one standard, lower-intensity model to the large majority of patients (perhaps 80%) who have minimal needs and several differentiated models for patients with additional needs (perhaps 20%), who may need higher or lower intensity models, realistic? If so, how should providers determine which patients have additional needs, how many of such patients are there, do their needs change over time, can patients successfully self-select into the appropriate model, how harmful are "mistakes" in model assignment, and what would the cost of this approach be? (Question evolved during post-paper discussions.)
6. What are the programmatically important differences between naïve initiators and re-initiators that should be incorporated into new models of care?

The questions outlined in the published paper and above are not mutually exclusive—evidence to answer them will overlap and may suggest revisions to the questions themselves. We believe that the five questions listed above provide a good starting point for our research, however. We will address each question separately for new initiators and re-initiators, as the answers may differ between these two populations.

We propose to pursue this research agenda through a combination of 1) analysis of existing data; 2) enrollment of a prospective cohort of ART initiators to evaluate preferences, needs, and triaging potential; 3) consultation with patients and providers to develop one or more new models of care; and 4) a pragmatic evaluation of the effectiveness and cost-effectiveness of the new model(s) in improving early retention rates. Activities 1 and 3 will consider all of sub-Saharan Africa; activities 2 and 4 will take place in South Africa and Zambia. (Zambia remains a tentative choice and can be reconsidered if necessary; it may also be possible to add a third country if wished.) We note that the focus of this project is the delivery of HIV treatment services, not the treatment itself; we will not conduct any work related to optimizing ARV regimens. The project will also include integrated capacity-strengthening activities to support the development of relevant research capacity in the project countries.

Objectives

The overall goal of this project, named Retain6, is to apply the principles of patient-centered design to inform recommendations for differentiated models of care for the first six months on ART for the WHO's global ART guidelines, PEPFAR's programmatic guidance, and national guidelines in sub-Saharan Africa. We hypothesize that 1) a majority of early patients will flourish with a lower intensity model, while a minority will need and/or want a more intense model; 2) both retention in care and resource allocation can be improved based on this premise; and 3) naïve and non-naïve initiators will have different needs that may require different models of care.

The project will have two phases, with an interim evaluation of results at the end of the first phase before entering phase 2. In Phase 1, we will develop practical models for offering more and less intensive services during the early treatment period, building on evidence of the effectiveness of current DSD models for established patients, the little research that already exists on the early treatment period, analysis of existing and new data, and broad consultation. As part of phase 1, we also aim to develop a practical public health approach for triaging newly initiating patients between more and less intensive models of care. In Phase 2, we will test and evaluate the new models developed, with the goals of improving retention in care for patients referred to both low- and high-intensity models while relying on the existing resource endowment available in project countries.

We anticipate that activities 1, 2, and 3 below can take place simultaneously in phase 1 (months 1-18), while activity 4 will be conducted in phase 2 (months 18-36) and will build on findings of from phase 1. Timelines may be pushed out if COVID-19 restrictions continue to hamper conduct of fieldwork.

Phase 1 activities (0-18 months)

1. Retrospective data

1a. The detailed, longitudinal data sets needed to understand the services required and provided during the first six months on ART are scarce but may exist. Using the published literature and clinicaltrials.gov records from 2018 to the present, which will generally reflect both pre and post-COVID-19 pandemic guidelines and practices, we will identify potential cohorts being followed during this period and will contact the researchers to ask whether their data will help answer our research questions and can be shared with us. We will also seek data to help estimate the proportion of patients starting ART who are non-naïve, though we expect such data to be scarce. This work will be limited to sub-Saharan Africa but not to any particular countries within the region. (We note that PEPFAR is making available extensive aggregate, cross-sectional data on both interruptions to treatment and returns to care, and we will incorporate these data where appropriate, while focusing our own efforts on more accurate and detailed cohort data.)

1b. The COVID-19 pandemic has led a number of countries to relax the requirements for entry into established-patient models of care and to allow multi-month dispensing during the first six months on ART[15]. Using the IAS's and CQUIN's databases of COVID-related changes made to treatment guidelines in Africa, we will look for "natural experiments" pertaining to the first six-month period that either have been evaluated by others or are accessible for evaluation as part of this project. For example, Malawi made 6-month dispensing available to patients after only 3 months on ART, rather than requiring 6 months' treatment experience, and an evaluation of this change may be feasible. It may also be possible to utilize the AMBIT project's existing, electronic medical record databases and/or sentinel site datasets from Zambia and Malawi for this analysis, though separating the impacts of the revised eligibility criteria from those of COVID-19 and other changes made in response to the pandemic (lockdowns, etc.) may be difficult. This work will focus on the AMBIT countries but include evidence from other countries if available.

1c. A priority to improve ART retention, both overall and in particular during the early treatment period, is to ensure that HIV services are delivered in conjunction with other clinical care that a patient may need, such as NCD treatment, family planning, and screening, prevention, and treatment for TB and advanced HIV disease. As part of the activities described above, we will seek existing data on non-HIV care that new ART patients receive[16], existing schedules for care for the most common co-morbidities, and existing service delivery models, so that new models for the first six months of HIV treatment can take these into account. This work will focus on South Africa and Zambia but include evidence from other countries if available.

1d. Finally, building on research already conducted by the AMBIT project, we will also review the published literature and conference presentations on early retention-related interventions that have already been implemented and evaluated. To our knowledge, no single intervention or model has so far "solved" the problem of high early attrition, but a number of approaches have been moderately successful for specific populations. These include approaches ranging from home-based ART delivery[17] to early multi-month dispensing (authors' data) to patient navigators[5]. We will also consider existing electronic opportunities to improve retention, such as electronic reminders and bot-based support (e.g. https://influencermarketinghub.com/whatsapp-chatbot-tools/, https://www.discovery.co.za/corporate/whatsapp-registration-journey, or https://triggerise.org/). From our review, we will create an initial inventory of potential interventions that can provide a starting point for Activity 3, described below.

2. Prospective cohort

As noted above, the model of service delivery for patients in their first six months on ART continues to be largely a "one-size-fits-all" approach, regardless of the individual patient's condition, history, concerns, resources, and other characteristics. Early treatment could be improved if patients could be triaged to receive more or less support based on a combination of known risks to retention in care and patient preferences for how little or how much interaction, and what kinds of interaction, with the health system are desired. We propose to combine the PREDICT project's patient profiles with a patient preference survey to develop a triage and referral tool for the early ART period, with different versions of the tool for naïve and non-naïve initiators. To the extent practical, we will take advantage of the AMBIT project's existing relationships with healthcare facilities (AMBIT sentinel sites) to facilitate creating a prospective cohort of initiators.

2a. The PREDICT project, a collaboration among HE^{2}RO, Boston University, Palindrome, and Right to Care, is using large patient-level data sets and machine learning approaches to develop tools to triage patients to groups with higher and lower likelihood of missing their next scheduled clinic visits or medication pickups. This approach is being validated in several ways. First, during model building, the predictive algorithms are trained on a "seen" data set where the algorithm has access to both positive and negative outcome data to develop predictive accuracy. After training the model, predictor variable data from the unseen test set are then given to the model and each predicted outcome scored against known outcomes. We then estimate performance metrics for each model in terms of sensitivity, specificity, positive and negative predictive value, and area under the curve (AUC) [18]. The model was able to correctly predict attendance in a range of 66-79% of scheduled clinic visits and VL suppression in 76% of viral load test results. We demonstrated high specificity (94% and 95% for the retention and VL models, respectively) and sensitivity >60% for both models, indicating that potentially low risk patients are readily and accurately identified by the model. Our goal is to identify low risk patients who can be cleared of need for intervention at that visit. Second, the approach was evaluated on a much smaller blind dataset from the SLATE I and SLATE II trials and demonstrated similar model performance results [19]. Currently, the model is being evaluated on

large provincial datasets in South Africa covering different geographic population groups from those used to build the original model.

With the addition of data from our SLATE trials and other studies, PREDICT has been able to focus on new ART initiators and create profiles or "behavioral phenotypes" of those most likely to miss each scheduled clinic visit during their first six months on ART. Each profile segments the population of patients into specific combinations of indicators of healthcare history, demographic features, and behavioral characteristics of a group of patients with similar probabilities of missing their next visit (and therefore—presumably—similar susceptibility to interventions targeting those characteristics)[20]. While risk profiles have been created before[21,22], PREDICT's strategy differs from traditional tracing, tracking, and other loss-to-follow-up interventions by identifying and referring at-risk patients *before* they are lost, while it is still possible to help them onto a different course, rather than waiting until they have already defaulted from care. This approach mirrors that of the SLATE studies, which created an algorithm to assess a patient's risk of a negative outcome if offered same-day ART initiation.

i. We will first undertake a review of whether and how risk-triaging has previously been used in primary healthcare clinics in Africa and the features that make this approach most likely to succeed. Previous risk scores developed to improve HIV outcomes (e.g., [23,24]) have not been adopted for widespread use in sub-Saharan Africa. Risk triaging is a common feature of clinical care in upper income countries for other chronic conditions, however, with mixed evidence on effectiveness in improving health outcomes[25]. A triage tool designed specifically for HIV care providers in primary health clinics, relying solely on indicators already collected or very easily added to routine data collection in standard of care, not dependent on access to resources such as networked computers or smart phones, and with very clear and specific follow-up actions may overcome barriers to adoption in sub-Saharan Africa.

ii. We will summarize our findings about the potential value of risk triaging in a project report and, if warranted, a journal publication. We will then convene a one-time review panel to consider our findings and PREDICT results to date and determine whether the next step should be further development of PREDICT, as described below. We anticipate that the review panel will include senior members of the RETAIN6 team, potential users of PREDICT (e.g. clinic managers and/or HIV program officials), representatives of international organizations with an interest in service delivery (IAS, WHO, PEPFAR), and BMGF representatives. If the review panel concludes that this is not a practical approach for routine care, or if current, preliminary PREDICT work is not promising, we will consider other strategies to triage patients for interventions.

iii. Depending on the results of the review described above and findings from the pilot PREDICT evaluation (BIT) currently underway within the Indlela project (https://indlela.org/prioritizing-retention-efforts-using-data-intelligence-and-cohort-targeting-in-south-africa/), we will enroll a prospective cohort of ART initiators, stratified between self-reported naïve and non-naïve patients, and arrange for existing clinic staff (if possible) to collect the minimal additional data needed to use the PREDICT triage tool during at least two interactions with each cohort participant. We will then observe outcomes for up to approximately 8 months to evaluate and improve the accuracy of the PREDICT algorithm in predicting next-visit completion in a real-world setting for these populations of patients. We will also explore patient-level changes over time in the probability of missing one's next clinic visit (or DSD model interaction), as preliminary PREDICT analysis has demonstrated that a patient's likelihood of missing the next visit can change from one period to the next. Depending on data availability, this activity may take place only in South Africa or in both project countries.

2b. At the same time, with the patients in the prospective cohort, we will conduct a survey of patient characteristics, needs, preferences, and risk perceptions with regard to retention in care and amounts and types of support desired during the first six months. To our knowledge, new or re-initiating ART patients have not been widely asked "how often do you want to come to the clinic?" or "where would be the best place for you to receive services—at the clinic, somewhere else in the community, at home, or remotely (phone)?," or "how much or what type of counseling do you believe you need?," or "what kind of model or intervention would work for you personally?" Because the cohort will include samples of both naïve and non-naïve initiators, we anticipate generating answers to these questions for both populations.

We anticipate using survey results in real time to improve the PREDICT algorithm iteratively, as we progress with the survey. The survey may take the form of a discrete choice experiment (DCE), as has been done by others for patients already in DSD models[26,27], or a survey of preferences and motivators/demotivators, depending on what is determined to be most useful for intervention design and/or complementary to what is already being done by other researchers. We anticipate that this survey will give patients an opportunity to identify both barriers and the specific types of assistance they would need to overcome those barriers. With the responses to this survey, we hope to be able combine data on clinic visit and refill histories; barriers and facilitators to retention; and patient preferences for interventions to identify programmatically useful population groups which can be incorporated into PREDICT and for whom models of care can be designed.

We note that this survey could also look forward to patient preferences for newer treatment delivery technologies, such as long-acting injectables. If a DCE is conducted, we will also use HE^{2}RO's TRANSLATE conceptual model to identify a subset of interventions that 1) appear likely to be effective, based on the DCE; 2) are feasible in that they focus on modifiable rather than non-modifiable attributes of service delivery; and 3) are affordable[28].

To help understand how patients' preferences and needs may change during the early treatment period, we will aim to enroll in this survey patients who are at different time points in the early treatment interval and/or administer the survey more than once to the

same patients (longitudinally). It may make sense, for example, to generate survey responses that reflect participants' views at 0 months, 2 months, and 6 months after initiation. We will also stratify this analysis by prior ART exposure (naïve v non-naïve patients), to understand the behavior of each group separately.

Finally, one topic of focus for the survey (and the prospective cohort) overall will be to understand the role of health and treatment literacy in improving short- and long-term retention in care. Lack of health literacy overall is associated with poor treatment adherence and negative health outcomes in numerous chronic diseases, including HIV[29,30]. There is still insufficient evidence available, however, about what constitutes "literacy" when it comes to retention in HIV treatment. Our previous work in South Africa, on the ENHANCE[31] and SLATE[32] studies, for example, suggests that patients generally perceive current counseling as inadequate and would like "more," but it is unclear what "more" would entail and whether it would actually improve outcomes, including patients' experiences. Other recent research, some by our group, suggests that patients' level of knowledge about HIV and ART is already relatively high, but that more knowledge does not equate to better adherence[33,34]. There is little evidence that the existing national adherence guidelines in South Africa (or their equivalent in Zambia) have identified the optimal combination of timing, content, and delivery mode for education and counseling, even if perfect fidelity to guidelines could be achieved. An under-emphasized component of current treatment literacy, for example, is explaining the concept of U=U; there is some evidence that better understanding of this would improve retention[35].

In Retain6, we will focus on determining the quantity and types of "informational interactions" (counseling and education) that can best retain patients on ART both short- and long-term. We will use the prospective survey to evaluate patients' level of health, HIV, and ART understanding both as they start treatment and over the course of the early retention period and to understand which specific aspects of current practices are considered helpful and which are not. As a starting point, we will draw on the Integrated Model of Health Literacy[36]. This model suggests that we should include in the survey questions that capture both how people currently do and how they would prefer to 1) access health information, including the source and format; 2) understand or comprehend that information; 3) appraise or judge that information; and 4) apply that information in their health decision making—in this case, retention on ART. Models of care we design for the first six month period can then incorporate this information for each patient segment or profile, on the assumption that different groups of patients will prefer and need different quantities and types of informational interactions.

We note that we do not anticipate being able to identify in Retain6 the optimal content for informational interactions, as this is likely to require a separate study of its own. We will, however, incorporate both existing and new findings about how to make counseling and education more valuable into the new model(s) of care that are evaluated in Phase 2.

2c. With the same prospective cohort, we will also:

i. Collect data on patients' use of healthcare and other support and resources during this period, to fill in gaps in the data collected under Activity 1.

ii. Collect biological specimens (dried blood spots and/or other samples) to identify previous exposure to tenofovir (TDF) and validate patients' self-reports on whether they are new initiators or re-initiators. We will implement a methodology similar to that described by Mavhandu-Ramarumo et al (2021)[37] and Sithole et al (2021)[38], using a local laboratory for sample analysis. Since non-disclosure of prior treatment experience is common, this analysis will improve our ability to stratify all aspects of the cohort study into naïve and non-naïve patient groups.

3. Development of models for early period

The evidence based developed in Activities 1 and 2 is intended primarily as a means to an end, not an end itself. The end we are aiming for is to develop effective models of care for the early ART period, where a model is a package of tailored interventions and procedures defined by the widely-used "building blocks" of DSD models: population served, locations and frequency of interactions, provider cadres involved, and specific services provided. Activities 3 and 4 use the information generated in the prior activities to develop such models.

3a. To identify and develop one or more models of care for the first six month period, we will conduct interviews and/or focus groups with naïve and re-initiating patients, clinical staff and other providers, program implementers, and policy makers to deepen our knowledge base about how treatment is delivered in the first six months, non-HIV care that should be integrated with ART, patients' and providers' perceptions of challenges and barriers to improvement, and what types of changes in guidelines they recommend and/or would be comfortable with. Interview participants can be selected from AMBIT sentinel sites and partners to facilitate access. We are particularly interested in learning patients' own perspectives on what would constitute an optimal model of care, following the principles of patient-centered care.

3b. A number of other BMGF-supported projects, and projects from other funders, are also working on components of the HIV cascade of care in South Africa and neighboring countries. These include, among others: Indlela (behavioral economics and health-seeking habit formation); the HSRC (populating the non-linear cascade in South Africa); PSI (testing, linkage, and retention for men); IDEal (linkage and early retention in Malawi); ENCORE (analysis of national treatment cohort in South Africa); INTUIT (role of U=U knowledge in uptake and retention); and various other studies. We will collaborate with these and other projects to ensure that activities in both phases of Retain6 are complementary to work that is already underway and that Retain6 leverages, rather than duplicates, these investments.

3c. Reviewers of the paper mentioned above, which presented a research agenda for designing models of care for the first six months on ART, rightly noted that the roundtable that developed the agenda included few implementers or researchers from LMICs. This was an artifact of the roundtable context—it was designed as a pre-CROI meeting, limited to CROI participants—but is certainly a weakness of the published agenda. In part due to COVID-19, as mentioned above, guidelines and procedures for ART delivery have also changed over the course of the past year.

To address these shortcomings, we will convene a series of roundtables that include clinicians, program implementers, MOH representatives, and patient representatives from the project countries, to re-consider the research agenda, review what is known about interventions for the early treatment period, and propose new intervention ideas. These roundtables will follow the lead set by the MATI workshop in 2015, which led to the SLATE studies and generated other evidence and multiple publications on ART initiation.

3d. We are aware that a number of other projects are underway that are relevant to Retain6's goals, including those mentioned above (activity 3b) and others. To ensure that new knowledge is shared across these projects in a timely way, we will host a semi-annual information exchange to bring together those who are implementing these projects to present and discuss their findings and brainstorm solutions to common problems. To avoid duplicating efforts, our preference is not to create a new platform for these meetings, but rather, if possible, add a new component to the IAS's Global DSD Research Collaborative and/or CQUIN's regular events or take advantage of other existing fora.

3e. Strengthening the capacity of our partner organizations to conduct the kind of research and evaluation called for by Retain6 is a high priority. We will plan to support at least two local researchers in each project country to complete a master's or doctoral degree in health economics, health systems research, data analysis, implementation science, or another relevant discipline over the course of the project, with both tuition support and protected time. In addition, we will support local project staff and collaborators to complete hands-on internships or fellowships on data management or analysis, conducting health systems implementation research, research writing, etc. If a need for specific skills is identified, short courses may be offered by our senior team, which has extensive experience in training in these areas; by our universities (BU and Wits); or through existing external programs offered by others. Where possible, we will take advantage of the CQUIN annual meeting, IAS conferences, and/or other relevant events to offer capacity-strengthening opportunities. We will develop a capacity-strengthening workplan during the first six months of Retain6 to maximize the benefits of the project for local capacity.

Phase 2 activities (19-39 months)

4. Interim decision

Activities in Phase 1 aim to identify and describe patients at higher-than-average risk of loss to follow up during their first six months on ART, understand their needs and preferences, and design models of care for this period. Phase 2 will start with a joint review and decision by the funder and project team regarding the value and feasibility of proposed Phase 2 activities based on the findings of Phase 1. The specific activities pursued in Phase 2 will depend heavily on the status of ART programs at the end of Phase 1 and whether new models are already being routinely implemented for the first six months on ART.

- If one or more novel models has been designed in Phase 1 that appears promising for implementation and evaluation in Phase 2, we will aim to both implement and evaluate the model(s), as we did with SLATE I and SLATE II. To assess whether a model should be considered "promising," we will utilize standard implementation science dimensions such as provider and patient feasibility, adoptability, acceptability, and affordability. We will ask a small group of stakeholders to review the results of this evaluation for each model that has been proposed to debate each model's potential to achieve project goals. Based on the views of both internal and external stakeholders, a decision will be made as to whether and how to proceed with Activity 5.
- If models that are consistent with the key components of an optimal model (as identified in Phase 1) are already being implemented by national HIV programs and/or implementing partners, we will aim to evaluate and compare these, consistent with the methods being used for DSD models for stable patients in AMBIT.
- If neither of these approaches appears to be of value, a decision about specific further activities will be made at this time.

5. Implementation and evaluation of models

Activity 5 described below is illustrative of what might be done in Phase 2. We anticipate that this activity will be a mixed-methods, experimental or quasi-experimental evaluation that captures patient outcomes, implementation feasibility, and cost-effectiveness. The detailed study design will be dependent on Phase 1 results and on site and data access at the time of implementation. The goal of this activity will be to identify one or more models of care for the first six-month period that improves both early and longer-term retention in care, is feasible to implement, is acceptable to both patients and providers, and is affordable with existing clinic resources.

We will work with clinic staff to implement the new models at a small number of healthcare facilities and compare the results of the new models, in terms of retention in care at 6 and 12 months and other outcomes, to what we observe at AMBIT sentinel sites that have not implemented the new models. This activity will be developed midway through the project, as it will depend on results of earlier activities to determine how it should be done. Principles for any new models of care tested in this project include that they 1) be feasible to implement on a large scale in typical, resource-scarce, public sector clinics in sub-Saharan Africa and require few if any additional resources beyond the existing budgets and capacities of primary health clinics; 2) reflect differences among facilities, geographic areas, and programs, in

terms of existing capacity and outcomes, patient load, characteristics of the patient population, etc.; 3) reflect the trend toward higher proportions of non-naïve patients among ART initiators; and 4) take into account newer findings from the behavioral sciences about incentives, motivation, and habit formation[39], on the premise that investing early in good adherence patterns will have a long-term payoff. Longer follow-up (to 24 or 36 months) can be incorporated into the study design if early results suggest that it is warranted and resources allow.

Potential risks/challenges

We anticipate that the challenges and risks facing Retain6 will be similar to those encountered for our AMBIT project and SLATE studies. These include:

- Existing data availability. Activity 1a in Retain6 relies on access to existing data. We cannot know the extent and availability of such data until we begin work on the project. Unlike in the AMBIT project, we are not dependent on access to national electronic medical record data sets, but we are counting on cooperation from other researchers in sharing their data and intervention plans. We believe that we have sufficiently constructive relationships with colleagues in other institutions to make such sharing a reasonable expectation, but it will not be perfect.
- Natural experiment data availability. Activity 1b requires that we identify one or more completed interventions that have implemented new models of care for the early ART period and whose implementers have and are willing to share data with us. Given the many experiments that are being tried in response to COVID-19, it is plausible to assume that we will find such opportunities, but there is no guarantee.
- Activities 2 and 4 will require research ethics approval prior to implementation. Obtaining such approval can delay activities unexpectedly. We will address this risk by planning ahead as far as possible and incorporating local IRB review schedules into activity timelines.
- As we have experienced with both AMBIT and the SLATE studies, national policies for the conduct of research and access to human subjects data can change over the course of a project. It is possible that changes will occur during Retain6 that will hinder or prevent some activities. We cannot prevent this, but we can ensure that Retain6 remains flexible so that we can adapt to policy changes as we go.
- A final risk to the success of this project is one faced by all implementation science activities—events move so quickly that research becomes out of date before it is finished. We expect models of service delivery to continue to evolve even as we are evaluating them. Our challenge, particularly when we reach Phase 2, will be to remain current and relevant while still generating rigorous results. We cannot control for this risk, but since we can expect it, we will design our activities to take it into account.

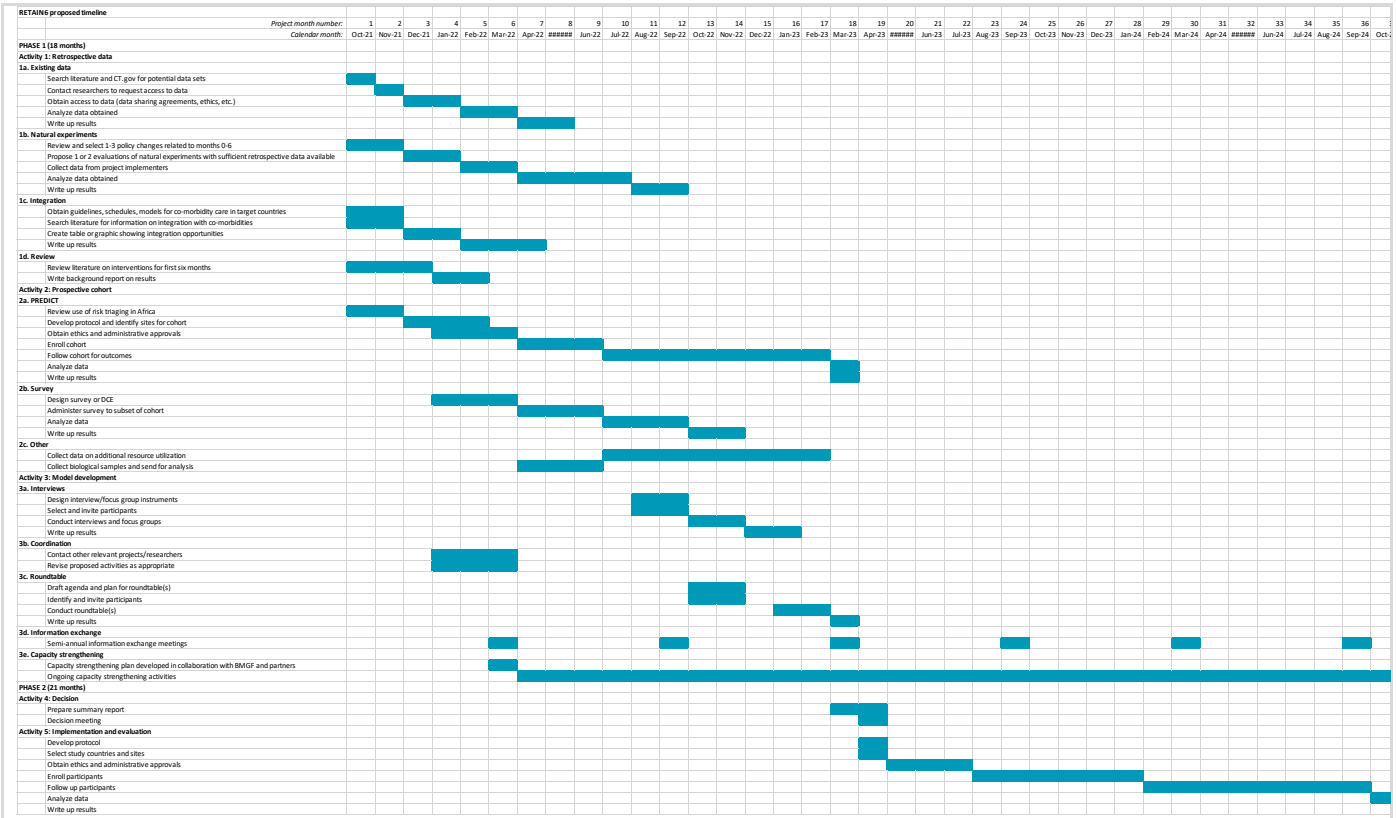
Organizational capacity

The three organizations proposed to conduct Retain6—CHAI-Zambia, HE^{2}RO, and Boston University—already have substantial capacity to carry out the activities in Phase 1. HE^{2}RO and BU have collaborated successfully for two decades. The staff complement at HE^{2}RO includes a core of trained data collectors and surveyors, data analysts, and researchers whose time will be allocated to Retain6 as needed. We expect to hire at least one additional local Senior Researcher to lead the in-country team, under the supervision of the Principal Investigator. All three organizations have collaborated for the past two years on the AMBIT project. CHAI-Zambia is committed to participating in Retain6 and will hire additional staff as needed to implement the project and will participate in capacity-strengthening activities.

Sustainability

The goal of Retain6 is to generate evidence about models of care that will result in better outcomes for patients in their first six months on ART. If successful, the project's results will be sustained by countries' adoption of the models and use of the evidence generated. Based on our experience with previous projects, we expect international guideline organizations and funders (WHO, PEPFAR, etc.) to use our results in designing their own recommendations and deciding which projects to fund. We also expect that Ministries of Health and implementing partners in both our project countries and others will incorporate our findings into their own guidelines and practices. We hope that this will be facilitated through, for example, the CQUIN network and local dissemination channels.

Timeline



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