Preferences for services in a patient's first six months on antiretroviral therapy for HIV in South Africa and Zambia (PREFER): research protocol for a prospective observational cohort study

Research Protocol

Preferences for services in a patient's first six months on antiretroviral therapy for HIV in South Africa

PREFER-South Africa

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Contents

1. SUMMARY OF PREFER-SOUTH AFRICA

With the advent of universal eligibility for HIV treatment ("treat all") and same-day and community-based antiretroviral therapy (ART) initiation, retention in care after a patient has started ART remains the main challenge to achieving optimal outcomes in HIV treatment programs. Consistently across both time and geography, the highest risk for loss from care is during a patient's first six months after ART initiation, with about quarter of all patients not retained by the end of month 6.

One of the reasons for the high attrition from care in this early retention period is that the model of care offered to most newly-initiating and re-initiating patients has barely evolved from its original outlines. Patients in their first six months on ART are generally not eligible for lower-intensity, patient-centered "differentiated service delivery" models that make remaining in care easier for experienced patients. Instead, most early 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.

This protocol is for the **PREFER-South Africa** study, an activity of the Retain6 project. Retain6 aims to develop new models of care for patients' first six months on ART. PREFER-South Africa will collect data on patients' characteristics, clinical and non-clinical needs, and preferences for different types of services during their first six months after initiating ART. We will conduct an observational, prospective cohort survey of newly-initiated or re-initiated adult ART patients at a selected set of 18 healthcare facilities in South Africa. Results are expected to inform the design of better models of service delivery for the early treatment period.

2. INVESTIGATORS

This evaluation will be conducted by investigators from the Health Economics and Epidemiology Research Office (HE^2RO) at Wits University in South Africa and Boston University in the U.S. Individual investigators are:

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3. BACKGROUND, RATIONALE, AND OBJECTIVES

a. Background

With the advent of rapid, same-day, and community-based initiation of antiretroviral therapy (ART) for HIV, the challenge of achieving optimal outcomes in HIV treatment has shifted even more fully onto retention in care 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]. 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[3], and attrition was 35.6% by 6 months in a recent observational study[4].

We speculate that there are several reasons for high attrition during the early treatment period, including both i) patient characteristics and ii) service delivery characteristics[5].

i) With regard to **patient characteristics**, after the World Health Organization (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[7,8]. The proportion of patients who are re-initiating ART after previously interrupting care is also climbing. A recent modeling exercise estimated that in 2020, fully 58% of those who test positive for HIV were already aware of their positive status[9] and thus may have declined an earlier opportunity to start or remain on treatment. Two small studies in South Africa identified ARV metabolites—evidence of recent exposure to ARV medications, in 53% and 19% of self-reported naïve ART initiators in Limpopo and KZN provinces, respectively. 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.

ii) **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[10]. While it offers many advantages, same-day initiation 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[11], 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.

b. Rationale

Despite the substantial changes in ART initiation and long-term service delivery described above, the model of care offered to most newly-initiating and re-initiating patients in South Africa has barely evolved from its original outlines. Both the latest WHO guidelines [14] and South Africa's National Adherence Guidelines[12] continue to recommend at least 6 months on ART as a prerequisite for eligibility for DSD models. 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. Reconsideration of how to deliver ART during the first six months and development of new models of care for this period are due[7].

A first step in designing new models of care for the early treatment period is to gain a comprehensive understanding of patients' needs, concerns, resources, and preferences for service delivery during this period. 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. In the PREFER-South Africa study, we will survey a sample of patients at various points between months 0 and 6 after ART initiation to develop a detailed profile of different groups of patients who may be best served by different models of care. We will take advantage of our research team's existing relationships with a sample of healthcare facilities to facilitate creating a prospective cohort of early treatment patients.

c. Objectives

PREFER-South Africa is a descriptive study that aims to generate detailed data about patients in months 0-6 after ART initiation in eight domains:

Domain I: Demographic and social characteristics

1. Demographic and socioeconomic characteristics, including education and employment
2. Household composition
3. Household economic status

Domain II: HIV testing history

1. Timing of first positive HIV test
2. Testing experience

Domain III: HIV treatment history

1. Time on ART
2. Previous experience with ART (for re-initiators)

Domain IV: HIV treatment experience

1. Current treatment experience
2. Adherence expectations
3. Disclosure

Domain V: Other healthcare

1. Co-morbidities
2. Other healthcare sought

Domain VI: Patient preferences

1. Preferences on how care should be delivered
2. Preferred format of information

Domain VII: Expectations of care

1. Patient's expectations for waiting time, etc.
2. Levels of satisfaction

Domain VIII: Costs of seeking care

1. Transport time and costs
2. Missed employment and wages

The survey will ask questions in each of these areas. Wherever possible, characteristics of ART-naïve patients will be compared to those of self-reported or confirmed ART re-initiators. Questions may be revised, refined, removed, or added based on data availability, Department of Health priorities, and other factors. The protocol will be amended whenever additional data, not described below, are needed.

4. STUDY DESIGN AND PROCEDURES

a. Overview

To collect the data described above, we will conduct a quantitative, structured survey of patients presenting at the study sites at any time beginning with the date of ART initiation (or re-initiation) and ending at 6 months after initiation. With written informed consent of participants, data provided

directly by patients (patient survey responses) will also be linked to their routinely-collected medical record data, which will be collected for the period from the first entry pertaining to the patient to up to 12 months after study enrollment to ascertain retention in care during the first months on ART. For a subset of survey participants, we will also collect dried blood spot samples to test for prior ARV exposure.

PREFER-South Africa is an activity of the Retain6 project (https://sites.bu.edu/ambit/the-retain6-project/), which focuses on designing new models of care for patients' first six months on ART. Retain6 is supported by the Bill & Melinda Gates Foundation and implemented by Boston University, the Health Economics and Epidemiology Research Office (HE^2RO) at Wits University, and CHAI-Zambia.

b. Study sites

PREFER-South Africa will be conducted at 18 sites (healthcare facilities and any associated service delivery) in 3 districts of South Africa. The study sites all previously participated in our SENTINEL and SPRINT studies. The sites were purposively selected based on availability ART patient volume, facility ownership (only public facilities were selected), and their variety of differentiated service models of HIV treatment. Due to our previous research at these sites, each site is well known to the study team, allowing us to leverage earlier findings and existing relationships with site staff. We note that these sites were selected to capture the variation among South African ART sites in terms of service delivery approaches, uptake, outcomes, costs, etc. They are not intended as a nationally representative group of facilities.

Table 1. Study sites for PREFER-South Africa

Facility	Setting	ART patients (TROA) as of August, 2021	Average ART initiates per month, 2021
West Rand District (Gauteng Province)			
Simunye Clinic (Westonaria)	Urban	1,783	16
Tarlton Clinic	Rural	1,803	17
Fanyana Nhlapo Clinic	Urban	1,897	16
Bekkersdal East Clinic	Urban	2,116	37
Zuurbekom Clinic	Rural	2,301	13
Krugersdorp Central Clinic	Urban	2,959	30
Ehlanzeni District (Mpumalanga Province)			
Msogwaba Clinic	Urban	6,365	49
Manzini Clinic	Rural	3,553	24
Legogote Clinic	Rural	1,946	9
White River Municipal Clinic	Rural	3,001	28
Nelspruit Community Health Centre	Urban	5,234	105
Kanyamazane Health Centre	Urban	5,523	43
King Cetshwayo District (KZN Province)			
Mandlazini Clinic	Rural	1,182	11
Ntuze Clinic	Rural	1,509	11
Umkhontokayise Clinic	Rural	2,231	10
Khandisa Clinic	Rural	3,361	23
Phaphamani Clinic	Rural	5,190	34
Richards Bay Clinic	Urban	7,934	34

c. Data to be collected

The study will collect four types of data.

1. Baseline survey at ART initiation. A structured questionnaire, designed for primarily quantitative analysis, will be administered to a sample of patients at each site. Identifiers will be collected to allow questionnaire responses to be linked to respondents' clinical records. Written informed consent will be sought from all participants, including consent to link questionnaire responses to clinical records and to collect data from clinical records. The questionnaire and consent information sheet and form are included as appendices to this protocol.

2. Medical record data. Using identifiers collected as part of the structured questionnaire, we will also collect follow up data from routine medical records for the period from the patient's initial data entry (first presentation for testing or care) to a maximum of 12 months after study enrollment (or a maximum of 18 months after ART initiation or re-initiation, as participants may be enrolled at any time up to 6 months after initiation). Medical record data will be drawn from Tier.Net (national EMR), paper records and registers maintained at the study sites, and other databases, such as the National Health Laboratory Services database to ascertain whether patients are retained in care during the first 6 months on ART.

3. Prior exposure to ART. While we will collect data on self-reported use of ART in the baseline survey, for a subset of patients, we will also collect a dried blood spot sample to use for testing for ARV metabolites to identify previous ARV exposure to compare this to self-reported use of ART. NHLS data will also be used to identify previous laboratory tests (e.g. viral loads) that indicate prior ART exposure.

4. Follow up information. Participants will be asked to consent to being contacted at any time during the 12 months following study enrollment for follow up questions and/or to be invited to participate in a focus group group discussion. Those contacted for follow up will be selected based on baseline survey responses (e.g. all participants who express specific concerns about treatment).

d. Recruitment and survey administration

We will recruit adult ART patients on treatment for ≤6 months who present at the study sites for ART initiation, routine care, or unscheduled care during the recruitment period. At the study sites, clinic staff will inform potentially eligible patients that they may be eligible to participate in a research study when the patient checks in at the reception desk. Patients who express interest will be referred to a PREFER research assistant, who will request verbal consent for screening. For those who provide verbal consent for screening, the research assistant will explain to each potentially eligible participant that a study is underway and that patients who voluntarily enroll in the study will be asked questions about their experiences with ART and preferences for services. They will be told that the study will have no effect on the care they receive; that they do not have to participate to continue to receive care at the site as they usually would; and that they do not have to answer any questions they do not wish to. The research assistant will enter patients who consent to screening in the screening register; those who are eligible and agree will then be administered written informed consent, and those who consent will be administered the survey.

Patients will be recruited consecutively as they arrive at the facility, based on availability of study interviewers. A trained PREFER-South Africa research assistant will administer the survey in person in a private location at the clinic. The consent process and questionnaire will be administered while patients are waiting for facility services (consultations or medication pickup). They will be assured that they will not lose their places in the queue as a result of study participation. Patients who start the survey but do not have time to complete it before reaching the front of the queue will be asked to return to the research assistant after receiving services, in order to complete the survey. We anticipate that each interview will last 75 minutes, including the consent process.

e. Biological sample collection

For a subsample of study participants who are enrolled on the day of ART initiation or re-initiation, a dried blood specimen (DBS) will be collected by finger prick to then undergo bio-marker testing to identify previous ART use. Specimens will be collected by the research assistants, who will be trained in safe and sterile collection techniques, as well as good clinical practice. Research assistants will administer a finger prink and assist the participant to collect the blood sample on a filter paper. A single DBS will be collected for each patient. Specimens will be allowed to air dry for 3 hours after being taken, or according to assay instructions. Specimens will be covered with glycine weighing paper after drying.

After preparation, specimens will be sent to an academic or commercial laboratory for analysis. The laboratory/ies to be used will be identified prior to initial sample collection, based on laboratory location, ease of sample transport, and costs. Specimens will be batch-screened for the presence of tenofovir diphosphate. Presence of TDF above 0.02μg/ml will be considered as positive for previous ART use in the previous 3 months or as advised by the laboratory.

The subset of study participants asked for a blood sample will be selected based on proximity of the facility (clinic) to a laboratory that has been contracted to perform the test. The subsample will be limited to participants who self-report no prior ARV exposure and will be stratified to capture participant characteristics (e.g. age and sex). Exact selection criteria will depend on clinic and laboratory procedures and requirements. We will amend the protocol to include these criteria prior to any sample collection.

f. Post-enrollment follow up

Participants will be asked during the consent process for their agreement to be contacted by telephone or e-mail at any during the 12 months following enrollment if further information is sought. During such follow-up, selected participants may be asked specific questions electronically, or participants with selected characteristics may be invited to participate in a focus group discussion. (For example, participants who indicated that they would have liked to receive more information about HIV during the ART initiation process may be invited to a focus group to discuss exactly what additional information should be provided.) Detailed procedures for and content of these follow up interactions will be submitted to the IRB as an amendment to this protocol prior to contacting any participants after enrollment.

g. Inclusion and exclusion criteria

Inclusion criteria for the PREFER survey are:

- Living with HIV and on ART for 0-6 six months at the study site

- ≥ 18 years old (18 and older considered adult for research purposes in South Africa)
- Presented at the study site for routine HIV-related care
- Provide written informed consent to participate.
- For patients providing a dried blood spot specimen, initiating or re-initiating ART at the study enrollment visit.

Exclusion criteria for the PREFER survey are:

- Unable to communicate in any of the languages into which the questionnaire has been translated or that is known to the research assistant
- Not physically, mentally, or emotionally able to participate in the study, in the opinion of the investigators or study staff
- Unwilling to take the time required to complete the questionnaire on the day of consent

Eligibility based on these criteria will be determined through completion of a survey screening form. The screening form will also allow us to compare the gender and age distribution of the population enrolled in the survey with those of the full potentially eligible population. The screening form is included as an appendix to this protocol.

h. Data entry, storage, and security

A screening register will be kept by the study research assistants to record the consent process and keep track of those who do not consent, to allow us to determine if our sample is biased by patient characteristics due to differential consent. The screening register will not contain any individual identifiers. It will request age category, gender, and months on ART, as needed to determine survey eligibility only. The register will be kept as a form on the screeners' tablets.

Patient survey responses will be entered into electronic databases at the time of interview, using tablets. If there are power failures, data will be entered onto paper study forms and then transcribed into a database at the local study office. Forms will be stored in a locked cabinet at the study sites, with access limited to the study team. Electronic data files will be stored on secure, protected drives at the Health Economics and Epidemiology Research Office (HE^2RO) in Johannesburg and at Boston University in Boston, with access limited to relevant study staff.

Survey CTO or a similar software program requiring secure log-in and access by invitation will be used to create an electronic database to manage quantitative study data. On a regular basis, the data will be converted to SAS, STATA, or R for final cleaning and data analysis. All analytic databases will be password protected with access restricted to the members of the study team.

All subjects will be assigned a seven-digit, sequential identification number. The study ID number will be used to identify individual subjects in the study databases and to link survey response data to patient retention outcomes data and for all data analysis. Linkages to retention outcomes data will be done under the direct supervision of PI Dr. Mhairi Maskew, who has been involved in the creation and management of datasets for research purposes for more than a decade. Once data are linked, identifiers will be removed from the analysis file and all subjects will be assigned a random study ID. A password-protected linking file allowing the anonymized data to be linked back to the identifiable data will be kept

in a separate file at HE^{2}RO only; it will not be sent to Boston University. In addition, all data files that are not anonymized will be password-protected, with access limited to authorized study staff.

HE^{2}RO has extensive experience not only with data linkage techniques but also with management and manipulation of patient-level data. Data will be stored on a local encrypted server in the HE^{2}RO office block. HE^{2}RO currently uses a Windows Server Standard Core Gen10 Intel Xeon Silver server. The security uses Microsoft Active Directory and ESET endpoint antivirus. Server access is restricted via standard Authentication and Authorisation policies. This server is physically secured in an access-controlled room, and only accessible virtually by designated persons with HE^{2}RO domain login credentials. Access to data storage folders on the server require an active HE^{2}RO domain user account. User access to folders are decided on a case-by case basis, and limited appropriately. Remote access is controlled by means of a Virtual Private Network, which also requires HE^{2}RO domain login credentials. The server is secured and maintained by the HE^{2}RO IT service provider. The network and server are monitored and maintained regularly by the IT service providers, and backed up onsite daily, and offsite on a weekly basis.

i. Data analysis

We will commence analysis with a descriptive summary of the demographic and clinical characteristics of participants enrolled in the study and responses to each question using frequencies and simple proportions for categorical variables and medians with interquartile ranges for continuous variables. We then stratify these baseline survey responses by site characteristics, time on ART, naïve v non-naïve treatment status, and/or patient characteristics such as age and gender, as data allow.

Utilising follow up data collected from patient medical records, we will conduct a crude analysis reporting simple proportions with 95% confidence intervals of patients achieving the retention outcome, defined as missing a scheduled clinical or medication pickup visit during the first 6 months after treatment initiation by more than 28 days. Next we will compare the proportions of patient disengaged from care by key varaiables including age, gender, clinical stage at ART initiation, site characteristics, time on ART and naïve v non-naïve treatment status.

The analysis will include a simple comparison of the groups with respect to baseline predictors of outcomes to look for any imbalances. These potential confounders include demographic and clinical variables, as well as geographic and facility-level factors (urban vs rural setting, facility type among others). We will then conduct a crude analysis comparing the proportion of patients achieving the dichotomous retention outcome by group and using a log-linear regression model, we will estimate crude risk ratios and crude risk differences and their corresponding 95% confidence intervals. Should any important imbalances be observed, we will proceed with an adjusted model. Should crude stratification techniques reveal potential effect measure modification, these analyses will not be adjusted but rather reported as stratified output.

5. SAMPLE SIZE

The sample size for the survey is 2,500 across the 18 study sites. We anticipate having the resources and time to enroll at each site for a period of 90 days. In 2021, an average total of 510 patients initiated (or re-initiated) ART at the 18 study sites per month. If 100% of these patients were retained in care for 6 months, then we would anticipate that the study sites have approximately 3,000 ART patients eligible for the study at any given time. Adjusting for an anticipated attrition rate of 30% by 6 months after

initiation, we estimate that there will be about 2,100 patients eligible for the study at the selected sites. As all of these individuals are within their first six months after treatment initiation, each is expected to visit the study clinic at least once during the three-month enrollment period.

As this is a descriptive study only and does not test a hypothesis, and all study procedures are minimal risk, we propose to enroll the largest number participants that is feasible during the enrollment period, with feasibility determined by frequency of eligible patients' clinic visits and interviewer capacity. Our maximum sample size for the survey is thus 2100, a number that we will round up to a maximum of 2,500 participants, in case facility volume increases in 2022 and 2023.

For this observational study, no assignment to treatment groups will occur, though we will stratify the retention outcomes analysis by the key variables described. Much variation exists in prevalence of both the outcome and exposures in the proposed analysis and there will thus be much variability in the differences that the proposed study sample size will be powered to detect. For example, if we consider the association of naïve and non-naïve ART status with disengagement in care, our prior work indicates that anywhere from 10% to 30% of scheduled visits are missed and that the distribution of naïve and non-naïve initiators at the study sites may be anywhere from 10% to 50%. Table 2 summarises the potential differences in retention between naïve and non-naïve initiators that our sample size would be powered to detect. Using a two-sided α of 0.05 and assuming a prevalence of missed visits to be between 10% and 30% among non-naïve patients, we estimate that we would have 80% power to detect a relative risk between 1.17 and 1.60, depending on the size of the stratified sample.

Table 2: Estimated detectable difference (expressed as a crude relative risk) stratified by prevalence of naïve initiators and retention outcome

Prevalence of naïve initiators	Prevalence of disengagement from care		
	10%	**20%**	**30%**
10% (n=250)	1.60	1.39	1.29
20% (n=500)	1.45	1.29	1.21
30% (n=750)	1.39	1.25	1.19
40% (n=1000)	1.37	1.24	1.18
50% (n=1250)	1.36	1.23	1.17

From among the patients enrolled in the survey, as described above, we will collect a dried blood spot specimens from up to 200 at a subset of the study sites, based on laboratory access and costs. The number of participants who will be invited for follow up data collection (additional questions and/or focus group participation) will depend on baseline and retention outcome results.

6. DISSEMINATION OF FINDINGS

The primary audience for the results of this study is the South African National Department of Health and its partners, which will use the findings to improve retention in care during the early treatment period. In addition, we will use the results to inform the design of one or more new models of service delivery, which we expect to implement and evaluate during a later stage of this project. Many of the findings will also likely be of broader interest in South Africa and other countries. Results of the study will be made as widely available as possible, through journals, websites, and conferences. Only aggregated, stratified data will be presented; it will not be possible to identify any individual patients from any of the results that are presented.

7. ETHICAL CONSIDERATIONS

The evaluation will require ethical approval from the Institutional Review Board of Boston University and the University of the Witwatersrand's Human Ethics Research Committee.

a. Potential risks and protections

Most data for this study will be drawn from questionnaires. As described above, we will collect a dried blood spot specimen from a subset of participants. This is a procedure that is routinely performed during HIV treatment and other primary care and carries little risk. We therefore believe that our study poses few physical risks to subjects beyond those routinely encountered.

We have identified three potential risks for patients participating in the survey.

Risk 1: Emotional distress

The patient survey will ask questions about health and other topics that could cause emotional distress among participants, who will have HIV and may have encountered obstacles in navigating the treatment process. Interacting with them in order to explain the study and confirm eligibility before requesting written informed consent may cause some emotional distress for some potential subjects.

Protection against Risk 1:

Study staff will be trained to identify distress among respondents. Site staff who introduce the study to potential subjects will be trained to assure potential subjects that referral to study staff and enrolling in the study are completely voluntary and that those who do not wish to enroll will receive exactly the same care as the study site would otherwise have provided. Potential subjects will also be told that they can discontinue participation even after consenting without any effect on their care. The distress protocol described below will be followed should any occur.

Risk 2: Loss of confidentiality

Patients participating in the provider survey will be asked for written informed consent. We will collect data indicating individuals' HIV status, their opinions on the quality of the services received, and some sensitive health information. A breach of confidentiality, for example through inadvertent loss of a storage device or paper files, would thus pose a risk to subjects.

Protection against Risk 2:

To protect patients against this risk, patient identifiers will be collected and stored separately from all other individual data. Identifiers will be entered on site and stored in encrypted, password protected files, so that no paper records containing identifying information are removed from the sites. Names, national identification numbers, and other identifying information will be used only for the purposes of linking disparate sources of data for the same patient (e.g. electronic medical record information to paper clinical records). As soon as a specific source document has been linked to the patient of interest, data from it will be entered in a record containing the Study ID number only. Analytic data sets will not

contain any identifiers, and the linking files containing the identifiers will be destroyed after linking is complete.

All study data, whether in electronic or paper format, will be stored in secure locations. Password-protected laptops or tablets used on site will be kept in locked and secure cabinets and rooms when not in use. Files will be transferred to the study office on a regular basis and stored on secure servers and in locked cabinets. Study staff will not be permitted to download de-identified data sets for cleaning or analysis except with the explicit permission of a co-investigator, and data sets will not be stored on individual hard drives when not in use. Upon completion of the study, computer files and any data collection forms containing study data will be retained for seven years and then destroyed.

All study staff will be trained in Good Clinical Practice, Research Ethics, and study procedures to ensure that they understand both research confidentiality requirements and study confidentiality procedures. Study investigators will monitor data collection on an ongoing basis. They will report to the BU IRB and the Wits HREC any breaches in confidentiality identified. In the event that a breach in confidentiality does occur, staff will be retrained on human subjects' protection and confidentiality if possible or removed from the study if either the breach is too serious or if the PIs feel the staff member cannot be sufficiently retrained. Staff will be made aware of this condition on employment.

Risk 3: Finger prick blood draw

A subset of participants will be asked to provide a small blood sample via finger prick. This procedure can result in brief discomfort or pain and in rare instances in bruising or infection[13].

Protection against Risk 3:

Research assistants will be trained in and practice drawing blood using finger pricks, including ensuring the use of sterilized equipment and applying pressure and a bandage (plaster) afterword. Participants who change their minds after consenting and do not wish to undergo the finger prick will be allowed to decline at the time it is offered. In case of an unanticipated level of bruising or bleeding, the participant will be referred to the clinic where the study is taking place to receive immediate care.

b. Distress protocol

During consent or questionnaire administration, if a patient exhibits distress reflective of what would be expected in an interview about a sensitive topic, study staff will offer support and extend the opportunity to: (a) stop the interview; (b) regroup; (c) continue. If a patient's distress reflects acute emotional distress beyond what would be expected in an interview about a sensitive topic, study staff will offer support and take the following actions: (a) stop the survey; (b) give the participant a quiet private space to regroup; (c) encourage the participant to contact his mental health provider, if they have one; if the participant does not have a mental health provider, provide the participant with a list of resources available including appropriate hotlines and referral to the appropriate person at the local clinic.

c. Direct benefits

There are no direct benefits to study subjects enrolled in this study.

d. Indirect (societal) benefits

The indirect benefits of this study are expected to be large. Attrition from care during the early treatment period is a major challenge to achieving HIV program goals in South Africa and elsewhere. Evidence that can improve service delivery models for this period has the potential to increase retention in care and thus improve overall treatment program outcomes and increase the efficiency of resource allocation.

Because the indirect benefits of the study are large and the risks to human subjects are minimal, we are confident that the benefits justify the risks.

e. Informed consent

Prior to screening for study eligibility, each potential participant will be read a verbal consent statement, which is included as the first section of the screening form (attached). Only those who agree to screening will be screened for study eligibility.The research assistant will complete a screening form to record study eligibility for each patient screened. The screening form will not collect any identifiable information pertaining to individual patients prior to receipt of written informed consent. For patients who agree to screening but decline to participate in the study (consent refused), the study interviewer will indicate the refusal and, if offered, reason for refusal in the screening form.

Written, informed consent will be sought from all eligible participants. Upon referral to the research assistant, patients will receive a more complete description of the study, including the details of why it is being done, the types of questions that will be asked, and the need for written informed consent. Patients will be assured that participation is voluntary and that they can withdraw from the study at any time, without affecting the quality of care provided by the site. They will also be offered the opportunity to ask questions. The informed consent information sheet will also explain that a finger prick blood specimen will be sought from some participants and the purpose for it and assured that they can refuse the finger prick if they wish. The patient will then be asked to provide written informed consent to participate.

The informed consent information sheet will describe the nature and goals of the study and assure subjects their information will be kept confidential. It will explain to subjects what will occur in the study and the procedures to be followed and/or questions to be asked. It will indicate that after the study has been completed, fully dis-identified data may be posted to a public research repository, as is typically required for journal publication. Participants will be offered a copy of the information sheet to keep if they wish.

The stamped consent form will be administered by a trained study research assistant. Participants will be assured that data collected for our study will be kept strictly confidential and will never be reported to clinic staff or anyone outside the study team.

The information sheet and consent form will be translated into Zulu and Sesotho, which are most commonly spoken by patients at the study sites. Translated consent documents will be submitted to required ethics committees for review prior to use with any study subjects.

f. Subject confidentiality

As explained above, we will take multiple steps to protect subject confidentiality. These are detailed in the paragraph entitled "Potential Risks and Protections."

g. Costs and payments

There will be no costs to subjects for participating in this study. Light refreshments (e.g. cool drink, biscuits) will be offered to participants during the interview in appreciation for their cooperation. Participants will receive compensation valued at R150 in the form of a shopping voucher or cell phone air time to thank them for their time and willingness to participate.

h. Access to data

As is often required by journals for publication of research manuscripts, we will post completely anonymized data sets to a public repository after all analysis and publication has been completed. The informed consent forms will alert participants to this and indicate that in providing consent to participate in the study, they are also consenting to the posting of completely de-identified data to a research repository.

We note that all data access procedures and policies at HE^2RO are Protection of Personal Information (POPI) Act compliant, under the supervision of the Wits Health Consortium.

i. COVID-19 considerations

In light of COVID-19 and the need to adhere to safety protocols to protect study staff and participants, we will implement the following precautions:

- Fieldwork will only occur when permitted according to the country's lockdown regulations.
- Training plans for the study team will be evaluated at the time and if COVID risk is too high, training will be done remotely via Zoom.
- We will supply personal protective equipment (PPE) material including masks, hand sanitizers, and/or other applicable PPE to the study team if recommended
- If any team members show COVID-19 symptoms, he/she will immediately report it to the study PI and action will be taken as specified in the COVID-19 SOP
- Study interviewers will capture responses directly onto tablets during the interview – therefore alleviating the need for printed questionnaires.
- Study interviewers will practice physical distancing (minimum of 1.5 meters apart) whenever possible while conducting fieldwork
- A separate COVID-19 SOP will provide detailed guidance on safety protocols that need to be followed while conducting fieldwork
- We will provide training on the COVID-19 SOP and procedures that need to be followed at the clinics/facilities, including infection prevention control measures and PPE use.

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9. APPENDICES

Data collection instruments

1. Patient survey instrument
2. Patient survey eligibility screening form (with verbal consent)

Consent forms and information sheets

3. Patient survey information sheet
4. Patient survey consent form