Tracing people living with HIV who are lost to follow-up at ART programs in Southern Africa: Study protocol	
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Background	<p>The successful treatment of people living with HIV (PLHIV) and the monitoring and evaluation of antiretroviral therapy (ART) programs both depend on regular and complete patient follow-up (1,2). Indeed, retention in care is an important component in the HIV prevention, treatment and care cascade and one of the key indicators used for the monitoring of ART programs. ART programs with high rates of loss to follow-up and poor ascertainment of deaths in PLHIV who are lost will underestimate mortality of all patients starting ART. Naïve survival analyses censoring patients lost to follow-up will be biased because mortality is assumed to be identical than among patients remaining in care (3). Analyses restricted to patients remaining in care will underestimate mortality among all patients who started ART.</p>

	Biased estimates of program-level mortality hamper the evaluation of single programs and the comparison between programs, settings and countries (4,5). Different methods are available to correct estimates of program-level mortality for loss to follow-up, including linkages of patients who are lost to ART programs to death registries, or, in the absence of such registries, tracing of patients lost to follow-up to ascertain their vital status (3,6–8). Such studies will be important in countries with limited, decentralized, or poorly functioning death registries.
Aims	To determine through tracing the status of PLHIV classified as lost to follow-up at ART programs that are part of the International epidemiology Databases to Evaluate AIDS in Southern Africa (IeDEA-SA); and thus to obtain accurate programs' retention in care and mortality estimates.
Hypothesis	Silent transfers and mortality are largely underestimated in routinely collected data from ART programs. The poor ascertainment of deaths, transfers and disengagement from care among patients lost to follow-up in ART programs impacts on the accuracy of estimates for retention in care and treatment outcomes, including mortality.
Objectives	<ol style="list-style-type: none"> 1) To trace PLHIV classified as lost to follow-up in IeDEA-SA participating ART programs in Lesotho, Malawi, Mozambique, Zambia, South Africa, and Zimbabwe to determine their status (alive or not, on ART or not) according to a standardized tracing procedure. 2) To estimate mortality and silent transfers among patients lost to follow-up by time from starting ART, by CD4 cell count at start of ART, by sex, and by age. 3) To estimate program-level mortality taking into account mortality among patients lost to follow-up, including for patients who stopped ART, interrupted ART or transferred to another ART program.
Methods	<p>Aim</p> <p>To trace a stratified random sample of approximately 500 PLHIV who are lost to follow-up at each participating ART program.</p> <p>Sampling procedure and eligibility criteria</p> <p>Prior to sampling, all participating ART programs will provide the IeDEA-SA datacenter at the University of Bern, Switzerland, with a list of all patients fulfilling the following criteria:</p> <ul style="list-style-type: none"> • Patient started ART before 01.01.2014 and was on ART on 01.01.2014 (i.e. not defined as lost to follow-up on 01.01.2014) or • Patient started ART between 01.01.2014 and 31.03.2017 (including) AND • Patient defined as lost to follow-up between 02.01.2014 and 30.06.2017 (including), meaning that the last time the patient was seen at the clinic is until 31.03.2017 (including).

The lists should provide the following variables:

- Clinic patient identifier (Clinic ART cohort number)
- leDEA patient identifier (ART number)
- Date of birth
- Gender
- ART start date
- Baseline CD4 cell count (if available)
- Date of last scheduled appointment (missed appointment)

From these lists, the leDEA-SA datacenter will randomly select 500 PLHIV to be traced at the corresponding ART program. In ART programs with less than 500 PLHIV classified as lost to follow-up, all will be selected for tracing.

The random sample will be stratified by sex (women and men), age at last visit (0–15, 16–25, 26–50 and ≥51 years old) and time on ART (≤30, 31–180, 181–364 and ≥365 days since ART initiation).

Tracing procedure

The tracing procedure will consist of the following steps:

1. Examination of patient files: Ensure that patient is truly lost to follow-up

2. Tracing

2.1 Text messages/SMS to arrange phone calls or home visits (if available)

2.2 Phone calls (if available)

2.3 Home visits (if available)

All tracing outcomes will be documented using the tracing form (see [Annexe: Tracing Form](#)).

Definitions

- ART: A regimen of at least three antiretroviral drugs
- Lost to follow-up: Lost to follow-up is defined following national guidelines as patients late for an appointment for ≥ 90 days (Malawi: ≥ 60 days), yet not classified as 'dead' or 'transferred-out'
- Tracing outcomes:
 - o Patient (or legal guardian or informant) found
 - Patient (or legal guardian) refused to be interviewed
 - Patient was transferred to another ART clinic
 - Self-transfer (i.e. undocumented or silent transfer)
 - Official transfer
 - Patient returned to care, or still in care at same clinic
 - Patient stopped taking ART
 - Patient never started ART although drugs were collected
 - o Patient (or legal guardian or informant) NOT found
 - Patient died
 - Patient traced and not found
 - Patient moved away
 - Patient reported to be alive through somebody else

Data collection, entry, management, and reporting

For the purpose of this research, data are collected on paper or on Android tablets using the tracing form (available in English and Portuguese), using the REDCap electronic data capture tool (www.project-redcap.org; see [Annexe: Tracing Form](#)) and transferred to the leDEA-SA Datacenter in Bern, Switzerland for analyses.

Statistical methods

We will use descriptive statistics to calculate the proportion of patients retained on ART, lost to follow-up, dead, transferred out.

The proportion of patients lost to follow-up successfully traced and found will be calculated.

Logistic regression models will describe differences between patients retained in care versus patients classified as lost to follow-up, and differences between patients traced and found versus traced and not found.

We will use weighted (weights determined according to sampling strategy) survival models to estimate mortality among patients lost to follow-up by time on ART, sex, age and CD4 cell count. A two-stage weighting procedure will then allow to estimate program level mortality, stratified by CD4 cell count, age, and sex.

Results will be used to correct program-level estimates of mortality. Other approaches will also be considered and user-friendly interfaces (nomograms, web calculators, graphical user interface etc.) will be developed to allow the ART programs to easily estimate the mortality among their patients lost to follow-up.

	<p>Ethical considerations</p> <p>This project has been approved by the Kantonale Ethikkommission in Bern (KEK) as part of leDEA-SA core activities.</p> <p>Tracing is part of routine care and therefore, all participants (or legal guardians) consented to be traced if needed upon ART initiation.</p> <p>The data will be used according to the highest legal and ethical standards and as such, significant effort will be devoted to ensure compliance with all national and international regulations and guidelines for human research. Collaborators accessing the data received mandatory training on Protecting Human Research Subjects and Information Security Awareness.</p> <p>All received data will be stored on secure servers at the University of Bern. Only individuals who work with the data, will have access to the data. The study dataset is coded and protected prior to transfer to the leDEA-SA Datacenter in Bern, Switzerland.</p>
Ownership of data	<p>Each ART program retains ownership of their original data throughout their participation and is able to analyze and submit publications on their own data. For the purpose of this study, the leDEA-SA Datacenter in Bern, Switzerland will analyze the collected data and submit publications in collaboration with the ART programs.</p>
References	<ol style="list-style-type: none"> 1. Geng EH, Odeny TA, Lyamuya R, Nakiwogga-Muwanga A, Diero L, Bwana M, et al. Retention in Care and Patient-Reported Reasons for Undocumented Transfer or Stopping Care Among HIV-Infected Patients on Antiretroviral Therapy in Eastern Africa: Application of a Sampling-Based Approach. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016 Apr;62(7):935–44. 2. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health TM IH. 2010 Jun;15 Suppl 1(s1):1–15. 3. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018 Nov;67(11):1643–52. 4. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS Med. 2011/01/27 ed. 2011 Jan;8(1):e1000390. 5. Anderegg N, Hector J, Jefferys LF, Burgos-Soto J, Hobbins MA, Ehmer J, et al. Loss to follow-up correction increased mortality estimates in HIV-positive people on antiretroviral therapy in Mozambique. J Clin Epidemiol. 2020 Dec 1;128:83–92. 6. Forster M, Bailey C, Brinkhof MW, Graber C, Boule A, Spohr M, et al. Electronic medical record systems, data quality and loss to follow-up: survey of antiretroviral therapy programmes in resource-limited settings. Bull World Health Organ. 2009/01/15 ed. 2008 Dec;86(12):939–47. 7. Etoori D, Wringe A, Kabudula CW, Renju J, Rice B, Gomez-Olive FX, et al. Misreporting of Patient Outcomes in the South African National HIV

	<p>Treatment Database: Consequences for Programme Planning, Monitoring, and Evaluation. Front Public Health [Internet]. 2020 Apr;8. Available from: https://pubmed.ncbi.nlm.nih.gov/32318534/</p> <p>8. Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, Beres LK, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. Rosen S, editor. PLOS Med. 2018 Jan;15(1):e1002489.</p>
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Tracing Form

Record ID

1. leDEA-SA Site

leDEA-SA site

- ☐ Lesotho SMART
- ☐ Malawi Dignitas
- ☐ Malawi Lighthouse
- ☐ Mozambique SMART
- ☐ South Africa Themba Lethu
- ☐ South Africa Hlabisa
- ☐ Zambia CIDRZ
- ☐ Zimbabwe SMART
- ☐ Zimbabwe Newlands

2. Information on tracer

Tracer identifier

(This code is specific to the tracer. The code should be provided by the site to ensure anonymity. Example: Tracer 1, Tracer 2, etc.)

Tracer background

- ☐ Nurse
- ☐ Social worker
- ☐ Health surveillance assistant
- ☐ Activist
- ☐ Field tracer
- ☐ Expert client
- ☐ Village health worker
- ☐ Lay counselor
- ☐ Other

Specify tracer background

3. Patient data

Patient identifier at the clinic

leDEA patient identifier

Gender

- ☐ Male
- ☐ Female
- ☐ Unknown

Is the date of birth known?

- ☐ Yes
- ☐ No, but age is known in years
- ☐ No, but age is known in months (for young children)
- ☐ No, unknown date of birth and unknown age

Date of birth (dd/mm/yyyy)

(If month and day are unknown, record 15 June; if only day is unknown, record 15)

Age in years

Age in months	_____
Caregiver details provided?	☐ Yes ☐ No
Relationship of caregiver to patient	_____
Village/community where patient lives	_____
District	_____
Province/region	_____
Time needed from patient's home to facility (one way)	☐ Less than 1 hour ☐ Up to half a day ☐ More ☐ Unknown
Name of health care centre, clinic or hospital attended by patient for HIV care	_____
Date of last visit, when patient was seen at the facility (dd/mm/yyyy)	_____
Date of missed appointment (dd/mm/yyyy)	_____
	(Record as much of the date as possible; if month and day are unknown, record 15 June; if only day is unknown, record 15)

4. Tracing log

Is the patient confirmed lost to follow-up?	☐ Yes ☐ No ☐ Unknown, patient file not found (END) (Definition lost to follow-up: Patient not seen for at least 90 days after the last missed appointment (60 days for Malawi Lighthouse and Dignitas) Definition END: No tracing can be done)
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A: Text message (SMS or other instant message) - one attempt only

Text message used to trace patient:	☐ Yes ☐ No
Date of text message sent (dd/mm/yyyy)	_____
Result (Wait minimum one day, but maximum seven days, for the patient's response)	☐ Phone call arranged by text message ☐ Home visit arranged by text message ☐ No response to text message ☐ Patient spontaneously returned to the facility after having received the text message ☐ Other (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)
Date when patient was seen at the facility? (dd/mm/yyyy)	_____

Patient spontaneously returned to the facility after having received the text message: result

- ☐ Patient/Caregiver was interviewed at the facility
- ☐ Patient/Caregiver will be called
- ☐ Patient/Caregiver will be visited
- ☐ Patient/Caregiver refused to be interviewed

B: Phone call - up to three attempts

Phone calls used to trace patients:

- ☐ Yes
- ☐ No

Attempt 1

Date of phone call (dd/mm/yyyy)

Attempt 1

Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 1

Phone call result

- ☐ Patient/Caregiver accepted to be interviewed on the phone
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Home visit arranged
 - ☐ Invalid number
 - ☐ No response, will be called again
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

Invalid number: Is there another number available?

- ☐ Yes
- ☐ No

Attempt 2

Date of phone call (dd/mm/yyyy)

Attempt 2

Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 2

Phone call result

- ☐ Patient/Caregiver accepted to be interviewed on the phone
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Home visit arranged
 - ☐ Invalid number
 - ☐ No response, will be called again
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

Invalid number: Is there another number available?

- ☐ Yes
- ☐ No

Attempt 3
Date of phone call (dd/mm/yyyy)

Attempt 3
Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 3
Phone call result

- ☐ Patient/Caregiver accepted to be interviewed on the phone
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Home visit arranged
 - ☐ Invalid number
 - ☐ No response
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

C: Home visit - up to three attempts

Home visits used to trace patients:

- ☐ Yes
- ☐ No

Attempt 1
Date of home visit (dd/mm/yyyy)

Attempt 1
Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 1
Home visit result

- ☐ Patient/Caregiver accepted to be interviewed
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Patient/Caregiver will be called at new number
 - ☐ Patient not localized at the given address or moved
 - ☐ Patient will be visited again
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

Attempt 2
Date of home visit (dd/mm/yyyy)

(Record as much of the date as possible; if month and day are unknown, record 15 June; if only day is unknown record 15)

Attempt 2
Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 2
Home visit result

- ☐ Patient/Caregiver accepted to be interviewed
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Patient/Caregiver will be called at new number
 - ☐ Patient not localized at the given address or moved
 - ☐ Patient will be visited again
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

Attempt 3
Date of home visit (dd/mm/yyyy)

Attempt 3
Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Attempt 3
Home visit result

- ☐ Patient/Caregiver accepted to be interviewed
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ Patient/Caregiver will be called at new number
 - ☐ Patient not localized at the given address or moved
 - ☐ Patient and nobody else found
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

D: Additional attempt (phone call or visit), in addition to the above-listed attempts (for instance, if new contact details were provided by a relative) - one attempt only

Additional attempt used to trace the patient:

- ☐ Yes
- ☐ No

Date of contact (dd/mm/yyyy)

How was the patient traced?

- ☐ Phone call
- ☐ Visit

Communicated with

- ☐ Patient
- ☐ Caregiver
- ☐ Relative
- ☐ Nobody
- ☐ Other

Other: Specify with whom the tracer communicated

Additional attempt result

- ☐ Patient/Caregiver accepted to be interviewed
 - ☐ Patient/Caregiver refused to be interviewed
 - ☐ No response (if phone call); Patient/Caregiver not found (if home visit)
 - ☐ Other
- (If you tick "Other", continue tracing log and use comment box at the end of the form to specify "Other".)

5. Tracing outcome

Tracing outcome (part 1)

What is the tracing outcome? (this should reflect the current patient state)

- ☐ Patient known to be alive
- ☐ Patient known to have died
- ☐ Vital status of patient unknown

Date of death (dd/mm/yyyy)

(If month and day are unknown, record 15 June; if only day is unknown, record 15)

Tracing outcome (part 2)

- ☐ Patient never missed a visit at the facility
- ☐ Patient returned to care at the facility
- ☐ Patient in care at another ART program
- ☐ Patient stopped taking ART
- ☐ Patient never started ART
- ☐ Patient/Caregiver refused to be interviewed
- ☐ Tracing attempted but patient and nobody else found

Patient in care at another ART program: Patient was transferred by

- ☐ Self-transfer or silent transfer
- ☐ Official transfer

Patient stopped taking ART: Date when stopped taking ART (dd/mm/yyyy)

(If month and day are unknown, record 15 June; if only day is unknown, record 15)

6. Patient's future intentions

Planning to return to the clinic

- ☐ Yes
- ☐ No, patient refuses to return to care
- ☐ Unknown

Patient refuses to return to care. Reasons (specify):

7. Patient's comments

Patient's comments

8. Tracer's comments

Tracer's comments