Does a verbal autopsy narrative provide accurate information about treatment defaulting for people who have died from HIV/AIDS? A data linkage study.

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CCVA	Computerised Coding of VA
CDA	Complete diagnostic autopsy
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COM	Circumstances of mortality
CDC	Centers for Disease Control and Prevention
CRVS	Civil registration and vital statistics
DHIS	District health information system
DNF	Death notification form
HIV	Human immunodeficiency virus
HPRS	Health Patient Registration System
HREC	Human Research Ethics Committee of the University of Cape Town
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ID	Identity document
LTFU	Lost to follow-up
MRs	Medical records
NCODV	National Cause of Death Validation
NDOH	National Department of Health
NOK	Next of kin
NPV	Negative predictive values
NSP	National Strategic Plan
PEPFAR	President's Emergency Plan for AIDS Relief
PCVA	Physician-Certified VA
PLHIV	People living with human immunodeficiency virus
PPV	Positive predictive values
ODK	Open Data Kit
SA	South Africa
SAMRC	South African Medical Research Council
STIs	Sexually transmitted infections
TIER.Net	Three Integrated Electronic Registers
TN	True negative
TP	True positive
UCOD	Underlying cause of death
UNAIDS	Joint United Nations Programme on HIV and AIDS
VA	Verbal autopsy
WHO	World Health Organization

GLOSSARY

Definitions of terms:

Adherence: "as the extent to which a person's behaviour is taking medication, following a diet, executing lifestyle changes and follows medical advice."

In antiretroviral therapy: "adherence is defined as taking the prescribed regimen of drugs in the right doses, at the same time, every day for a lifetime. This is a process that requires adjustment over time and across different aspects of one's lifestyle."

Non-adherence: "as the inability of patients to follow treatment plans, take medications at prescribed times and frequencies and also follow restrictions regarding lifestyles, food and other medications."

Lost to follow-up: when a patient has had 180 days or more since the last clinic visit.

Treatment 'defaulter: defined by the South African national TB management 2014 guidelines is a patient that interrupted treatment for 2 consecutive months or more.

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PART A: JOURNAL MANUSCRIPT

Does a verbal autopsy narrative provide accurate information about treatment defaulting for people who have died from HIV/AIDS? A data linkage study.

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ABSTRACT

Background

The South African National Cause-of-Death Validation (2017/18) project utilized the WHO 2016 standard VA questionnaire, which included both structured questions and an open narrative from the next of kin to describe the events surrounding deaths. An unexpected finding was the significant number of HIV/AIDS-related deaths mentioning treatment default in the narrative.

Objectives

This study aims to determine the accuracy of VA narratives in identifying ART treatment default by linking data from the national treatment register with NCODV 2017/18 HIV/AIDS related death data.

Methods

Secondary analysis of VA data from the NCODV 2017/18 project after linking with TIER.Net data on ART treatment maintained by the Department of Health. Agreement between treatment default identified from VA narratives and from TIER.Net was investigated using Cohen's Kappa (k), and the sensitivity and specificity of the narrative for identifying treatment default was estimated.

Results

Data linkage succeeded for 691 (58.9%) deaths, with 62 (5.3%) cases excluded due to inconsistencies. Among the 629 linked cases, 48.3% were identified as treatment defaulters in TIER.Net, compared to 29.4% indicated by VA narratives. The agreement between VA narratives and TIER.Net was 59.1%, with a Cohen's Kappa value of 0.17 (95% CI: 0.10–0.24). Sensitivity and specificity of VA narratives for identifying treatment default were 38.2% (95% CI: 34.4%–42.0%) and 78.8% (95% CI: 75.6%–82.0%) respectively, with positive and negative predictive values of 62.7% (95% CI: 58.9%–66.5%) and 57.7% (95% CI: 53.8%–61.5%) respectively.

Conclusions

The VA narratives were not sensitive enough to identify all treatment defaulters, likely related to the lack of structured questions related to defaulting but possibly also related to non-disclosure of HIV status and treatment. Of concern is the high proportion of deceased who had defaulted on treatment.

Keywords: human immunodeficiency virus, antiretroviral therapy, treatment default, lost to follow-up, verbal autopsy, data linkage, TIER.Net.

BACKGROUND

South Africa (SA) has the largest population of people living with human immunodeficiency virus (PLHIV) and the highest number of PLHIV on antiretroviral therapy (ART) worldwide (1, 2). In 2017, approximately 7.9 million PLHIV aged 15 to 64 were aware of their HIV status, with 70.6% receiving ART (3). The Universal Test and Treat 90-90-90 global target aims for 90% of all PLHIV to know their HIV status, 90% of those diagnosed with HIV to receive sustained ART, and 90% of those on ART to achieve viral suppression. This strategy has been adopted to eradicate HIV (4). PLHIV are started on ART as soon as they are diagnosed and are advised to remain in care, actively participating in ART programs to receive medication and have their HIV clinical indicators monitored at proper intervals to reduce mortality and infectivity (5-7). PLHIV are initiated on ART as soon as they are identified and are advised to remain in care and actively attend and participate in ART care programs to receive medication and to have their HIV clinical indicators monitored at proper intervals to reduce mortality and infectivity (6, 8). However, maintaining people on ART remains a challenge. A systematic review of cohort studies from sub-Saharan Africa found that one-third of patients on ART were reported as lost to follow-up (LTFU) or deceased within three years of starting ART (9). Since the inception of national HIV treatment programs, some studies have observed a decrease in the proportion of patients LTFU over time, while others have noted an increase in LTFU rates as the epidemic has progressed. This trend coincides with the growing number of patients registered at health centres providing ART (10-13). In a systematic review of studies on LTFU or default from ART care in South Africa, Kaplan et al. (2019) highlight the lack of clear definitions and standardization in measuring LTFU and retention. They also note biases in reporting interruptions in care, stemming from variations in reported outcomes (14). Fox et al. (2010) argued that clinics should consider using vital registration data to update outcome information for patients who are LTFU (15).

Verbal autopsy (VA) is a method used to determine the underlying cause of death (UCOD) through an interview with the next of kin (NOK) or another caregiver. This method involves a set of structured questions along with a free-text open narrative in the respondent's own words, detailing how the death occurred (16). It is typically used at the community and population level in countries with poor vital registration systems, where many deaths occur at home without contact with the health system (16). In South Africa, the National Cause of Death Validation (NCODV) project (17) made use of a VA and/or medical records for a national sample of deaths collected in 2017/18 to assess the validity of the reported UCOD submitted by doctors for death registration and used for vital statistics. The results from over 5,000 VAs collected for the NCODV indicated that 22.8% of the deaths were due to HIV/AIDS (17). An unexpected finding was that 10.2% of the narratives for deaths from HIV/AIDS mentioned treatment default by the decedent.(17).

The aim of this study is to assess the validity of information from the VA narrative regarding ART treatment default by linking data for deaths from the NCODV 2017/18, where HIV/AIDS was the UCOD, with treatment information reported in TIER.Net (18), an electronic patient monitoring system for HIV/AIDS patient visits developed in South Africa. The first objective is to determine the proportion of decedents that defaulted according to the VA narrative and according to TIER.Net. The second objective is to determine the level of agreement on treatment default between the VA narrative and TIER.Net. The third objective is to determine the sensitivity and specificity of treatment default identified in the VA narratives, treating the linked data (TIER.Net) as the gold standard.

METHODS

Study design and setting

South Africa has a population of about 60 million people and records approximately half a million deaths annually (19). When a death occurs, a doctor completes the medical certificate of cause of death on a death notification form (DNF), the DHA-1663 form, (20) which initiates the death registration process. A family member or funeral practitioner then takes the DNF to the Department of Home Affairs for the death to be registered and a death certificate issued. This descriptive study uses secondary data from the NCODV 2017/18 project, which collected and assigned UCOD to 5,375 VA interviews for a national sample of deaths that occurred between September 1, 2017 and April 13, 2018 in 27 selected health sub-districts in South Africa (17). The linkage was conducted by officials from the National Department of Health (NDOH) who manage the TIER.Net system. The NCODV deaths included physician-coded VA deaths assigned a UCOD of HIV/AIDS. Information on treatment defaulting was extracted from the narratives by searching for specific words and terms (Annexure 1). The records from narratives containing information on treatment default were compared with the outcomes in the TIER.Net data to verify the validity of the narrative information.

Study population

The VA reviews identified 1 196 with HIV/AIDS as UCOD. Deaths of infants and children ≤ 11 years were excluded, resulting in a study population of 1 174. The HIV/AIDS death records were sent to NDOH (TIER.Net) for data linkage.

Primary and secondary outcome measures

The primary outcome was the proportion of HIV/AIDS deaths who defaulted on treatment according to the combined information obtained from TIER.Net (treatment status) and VA narratives (date of death). The secondary outcome is to determine the sensitivity and specificity of treatment default identified in the VA narratives alone.

DATA SOURCES

Verbal autopsy

Funeral Parlors and the Department of Home Affairs offices serving the sampled areas were enlisted to inform the next of kin (NOK) about the study and seek their permission for the research team to contact them later. Trained fieldworkers then approached the NOK and made arrangements to conduct face-to-face VA interviews using the three questionnaires from the WHO 2016 instruments (21). These instruments were translated into South Africa's nine official languages, with efforts made to match the interview language to that of the respondent. Fieldworkers interviewed the NOK who had agreed to participate in the NCODV 2017/18 project and administered the WHO VA 2016 questionnaire after obtaining informed consent. The VA questionnaire collects information about signs and symptoms around the time of death, a brief medical history, and the utilization of health services. There is also an open narrative section where the NOK describes the circumstances leading to the death. KoBoTools was used to capture all responses and the narrative written out in text (in English) and later

captured as an image (jpeg). A team of study doctors then reviewed the responses and narratives to identify the UCOD which were then coded to ICD-10 for analysis. In addition, the doctors prepared a short medical history.

All the VA narratives were transcribed into Excel spreadsheets and the HIV/AIDS deaths were selected and read by the lead researcher (MM). Words and phrases such as "defaulting," "defaulted", "stop taking treatment", "top drinking tablets" etc that imply treatment default was incrementally added to a list used to identify defaulters from non-defaulters (Annexure 1 with all identified phrases).

A consolidated HIV status variable was generated for the VA data based on the following questions in the WHO 2016 VA questionnaire: "**Was an HIV test ever positive?**", "**Was there any diagnosis by a health professional of AIDS?",** and "**Did (s)he receive (or need) antiretroviral therapy (ART)?**" together with the physician summary variable "**HIV status**" that was based on their review of the VA. For this analysis, the decedent was categorised as "HIV positive" if any of the indicators had a positive result, otherwise the decedent was identified as "No indication of HIV."

Routine health information (TIER.Net)

In 2010, SA National Department of Health (NDOH) introduced an electronic patient management system that was used to monitor and evaluate HIV care and treatment programmes at facility level which was integrated into the district health information system (DHIS) for reporting various programme data from sub-district to national levels. TIER.Net has a three-tier approach: a paper-based system as tier 1, an electronic version of the paper register as tier 2, and full electronic medical record software at tier 3 (18). TIER.Net includes information on clinic visit attendance, laboratory results, and ART dispensing records for all patients on ART.

Treatment default definition:

TIER.Net considers a patient to be lost to follow-up (LTFU) when they have not attended the clinic for three months. This definition aligns with that described by Chi et al. (2011) (22) which defines LTFU as when a patient has had 180 days or more since their last clinic visit. This study will use the TIER.Net definition of treatment default.

Calculation of treatment default:

To determine if the decedent had defaulted on their treatment or followed-up on their treatment by attending clinic, two categories of time interval between successive visits ≤3months and ≥3months were created. By subtracting the date of death from the date since last clinic visit, the time interval, in months, was calculated in Excel as follows: (Dateofdeath - LastARTVisitDate) * 12/365.25

DATA LINKAGE

The NDOH, which manages the Three Integrated Electronic Registers database (TIER.Net), was approached to undertake the linkage with the 1,174 HIV/AIDS-related deaths. A password-protected Excel spreadsheet containing selected variables from the NCODV dataset was provided. These variables included the unique study identity number, gender, name, other names, surname, date of birth, identity number, place of residence, and province of death. An NDOH official performed the linkage and returned an anonymized dataset with 1,009 entries, consisting of multiple visits with information on every patient registered for ART at a health facility. This

dataset included details of each patient's visits to receive ART, such as the date, prescribed ART regimen, date of the next appointment, and the ART provider.

During the data cleaning phase, the HIV/AIDS and TIER.Net datasets were merged using the unique study ID. A decision was made to use only the last scheduled clinic visit, removing duplicate entries to determine monthly intervals for LTFU. This process resulted in 691 single entries with all relevant information; cases missing information or with the last clinic date captured after the date of death were excluded (Annexure 1, Figure 1).

Study size

During the planning of the data linkage study, different margin of errors and sample sizes calculations were considered for the estimation of a proportion as it was anticipated that not all NCODV cases will be linked with TIER.Net (https://www.calculator.net/sample-size-calculator.html). The calculations were based on an assumed proportion of 50% to provide the largest error margin. It was noted that a sample size of 560 would have a 3% margin of error on the estimated proportion with a 95% confidence interval (Annexure 1, Table 1), indicating that a study population size of 1 174 would be sufficient. Initial exploration of data linkage suggested that this sample size will be achievable.

STATISTICAL METHODS

Descriptive statistics (percentages) were used to summarize participants' characteristics. Characteristics were compared using Chi-square or Fisher's exact tests for categorical variables. A p-value ≥0.05 is considered to be statistically significant. Data management was undertaken using excel spreadsheets and data analysis was performed with Stata 15 (23).

The sensitivity and specificity analysis with their 95% confidence interval (CI) were compared for VA narratives and TIER.Net data as well as VA narratives and LTFU (≥3 months). The sensitivity refers to the ability for the VA narrative to identify treatment defaults whereas the specificity refers to deaths that were identified as non-defaulters from TIER.Net. The formula for the calculation were defined as:

$$Sensitivity = \frac{TP}{(TP\ + FN)}$$

$$Specificity = \frac{TN}{(FP + TN)}$$

The positive predictive values (PPV) and negative predictive values (NPV), are the proportions of positive and negative results in statistics and diagnostic tests that are true positive and true negative results (24), respectively with the following formulae:

$$Postive\ prediction\ value\ (PPV) = \frac{TP}{(TP\ + FP)}$$

$$Negative\ prediction\ value\ (NPV) = \frac{TN}{(TN\ + FN)}$$

***TP** = true positive; **FP** = false positive; **TN** = true negative; **FN** = false negative*.

ETHICAL CONSIDERATIONS

The NCODV 2017/18 protocol, outlining informed consent procedures, and including validation against disease registers, was provided ethical clearance approval by the SAMRC Ethics Committee (EC004-2/2017). This data linkage study was also approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 346/2022).

RESULTS

Participants

From the 1 174 HIV/AIDS deaths, it was possible to link 691 (58.8%) cases with data from TIER.Net. However, a further 62 (5.3%) cases were excluded due to inconsistent information (Annexure 1, Figure 2) leaving 629 (53.6%) cases available for the study. In total, the unlinked and inconsistent information cases accounted for 545 (46.4%) cases that were excluded from the analysis (Figure 1).

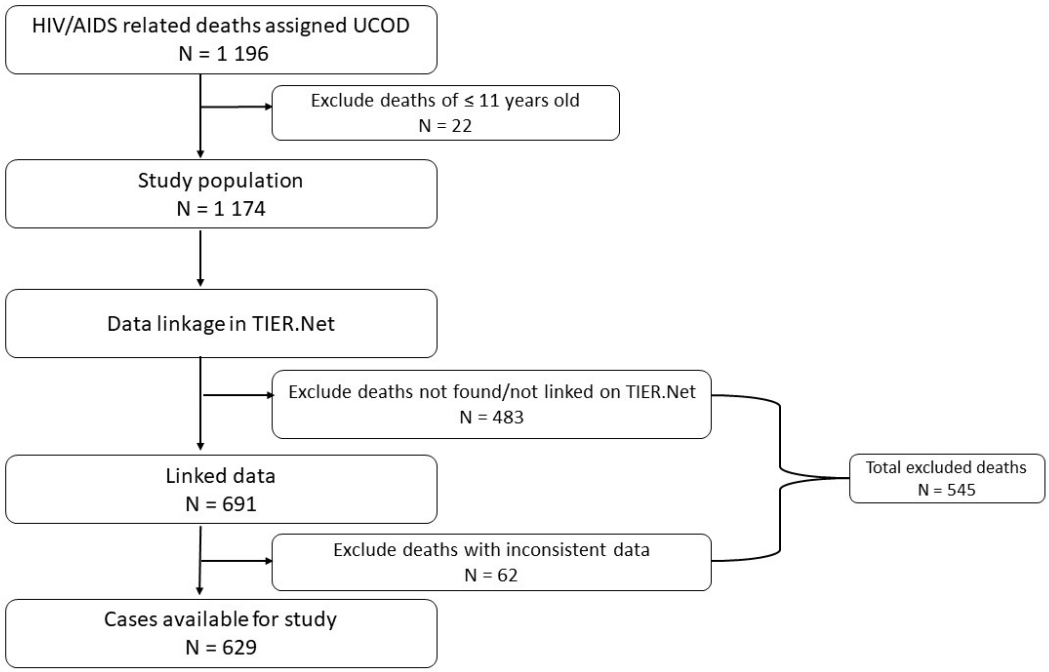

Figure 1: Flow diagram showing study population of HIV/AIDS related deaths linked in TIER.Net for this study.

Characteristics and linkage status according to TIER.Net

Table 1 linkage results showed no significant gender difference (p-value = 0.086) between the female 305 (48.5%) and male 324 (51.5%) linked cases versus female 237 (43.5%) and male 308 (56.5%) unlinked/excluded cases when comparing the overall HIV/AIDS cases. The study population was mostly from the Black African population group and the other groups were combined due to not having enough participants, the results showed no significant difference (p-value = 0.827) between the linked and unlinked/excluded cases. The age distribution of

the linked cases tended to skew younger, with individuals aged 12–44 years representing a significant portion of both the linked cases (380 cases, 60.4%) and the unlinked/excluded cases (290 cases, 53.2%). In contrast, the older population (45–65+ years) had fewer cases, with 249 (39.6%) linked and 255 (46.8%) unlinked/excluded, a difference that was statistically significant (p-value = 0.036). There was a significant difference by province and better linkage in the Free State 88 (14.0%), Eastern Cape 75 (11.9%), Northern Cape 64 (10.2%) and Western Cape 15 (2.4%) with poorer linkage in North West 134 (21.3%), KwaZulu Natal 111 (17.6%), Gauteng 38 (6.0%) and Limpopo 38 (6.0%), which was significant (p-value = 0.004).

Table 1: Characteristics of HIV/AIDS deaths and TIER.Net linking status.

Characteristics	Total 1 174 (100.0%)	Linking status		
		Linked 629 (100%)	Unlinked (Excluded) 545 (100%)	p-value
Gender				0.086
Female	542 (46.2%)	305 (48.5%)	237 (43.5%)	
Male	632 (53.8%)	324 (51.5%)	308 (56.5%)	
Population group				0.827
Black African	1 077 (91.7%)	576 (91.6%)	501 (91.9%)	
Other	97 (8.3%)	53 (8.4%)	44 (8.1%)	
Age groups				0.036
12 – 24 yrs	50 (4.3%)	33 (5.3%)	17 (3.1%)	
25 – 44 yrs	620 (52.8%)	347 (55.2%)	273 (50.1%)	
45 – 64 yrs	413 (35.2%)	207 (32.9%)	206 (37.8%)	
65+ yrs	91 (7.7%)	42 (4.9%)	49 (9.0%)	
Province				0.004
Eastern Cape	131 (11.2%)	75 (11.9%)	56 (10.3%)	
Free State	130 (11.1%)	88 (14.0%)	42 (7.7%)	
Gauteng	96 (8.2%)	38 (6.0%)	58 (10.6%)	
KwaZulu Natal	220 (18.7%)	111 (17.6%)	109 (20.0%)	
Limpopo	71 (6.1%)	38 (6.0%)	33 (6.1%)	
Mpumalanga	116 (9.9%)	66 (10.5%)	50 (9.2%)	
Northern Cape	115 (9.8%)	64 (10.2%)	51 (9.4%)	
North West	270 (23.0%)	134 (21.3%)	136 (24.9%)	
Western Cape	25 (2.1%)	15 (2.4%)	10 (1.8%)	

The high number of unlinked/excluded cases was a concern, prompting a review of the responses to the HIV/AIDS-related questions in the WHO 2016 VA questionnaire and the HIV/AIDS data from the physician review to assess the certainty that the study participants had HIV and confirm that they died from HIV/AIDS. When exploring the HIV definite variable, the results showed that 72 (13.2%) unlinked/excluded cases had no indication of HIV/AIDS, compared to 27 (4.3%) linked cases, a difference that was statistically significant (p-value < 0.001). Full details can be seen in Annexure 1, Table 2. This raised the possibility that some of the unlinked cases might not have had HIV.

Treatment defaulters according to VA narratives and TIER.Net

Initially, the VA narratives identified 10.2% treatment defaulters among HIV/AIDS deaths (17). Upon further investigation, more key phrases implying treatment defaulting were discovered resulting in 302 (25.7%) defaulters identified in the narratives. Of the 629 cases that were linked with TIER.Net, 185 (29.4%) cases were identified as treatment defaulters from the narratives and 444 (70.6%) were not. Among the cases that did not link, 117 (21.5%) were treatment defaulters and 428 (78.5%) were not treatment defaulters (Table 2). In our study, TIER.Net had recorded only 40.7% of the cases as RIP (deceased). However, after data linkage, it was confirmed that the entire study population had died. Full details can be seen in Annexure 1, Table 3.

Table 2: Treatment defaulters according to VA narrative and TIER.Net.

Characteristics	Total 1 174 (100.0%)	Linking status		
		Linked 629 (100%)	Unlinked (Excluded) 545 (100%)	p-value
Did the narrative indicate treatment default?				0.002
Yes	302 (25.7%)	185 (29.4%)	117 (21.5%)	
No	872 (74.3%)	444 (70.6%)	428 (78.5%)	

Agreement between VA narratives and TIER.Net

In Table 3, 304 (48.3%) linked cases were identified to be LTFU once the date of death was taken into consideration while 325 (51.7%) cases had received treatment within 3 months of attending clinic. The overall level of agreement between the VA narratives and TIER.Net was 59.1% with a Kappa statistic of 0.17 (95% CI: 0.1 – 0.2), indicating slight agreement beyond what would be expected by chance (Annexure 1, Figure 3).

The specificity, at 78.8% (95% CI: 75.6% – 82.0%), confirms that the VA narratives correctly identified non-defaulters. However, the sensitivity for identifying defaulters was poor at38.2% (95% CI: 34.4% – 42.0%). This is likely because information provided by NOK was voluntary and many did not indicate treatment defaulting in the VA narratives. In this study, a decedent who died from HIV/AIDS had a 62.7% (PPV) (95% CI: 58.9 – 66.5) chance to have defaulted and 57.7% (NPV) (95% CI: 53.8 – 61.5) not to have defaulted based on information in the VA narrative (Annexure 1, Figure 4).

Table 3: Description of treatment default cases in the narratives that were LTFU.

Did the narrative indicate treatment default?	TIER.Net– clinic attendance		Total
	Yes (LTFU ≥3 months)	No (Follow-up ≤3 months)	
Yes	116 (18.4%)	69 (11.0%)	185 (29.4%)
No	188 (29.9%)	256 (40.7%)	444 (70.6%)
Total	**304 (48.3%)**	**325 (51.7%)**	**629 (100.0%)**

DISCUSSION

Out of the 629 linked cases we observed that 29.4% (95% CI: 25.8% – 33.1%) had defaulted based on unsolicited information recorded in the VA narrative. However, following the data linkage with routine health information for management of HIV/AIDS treatment (TIER.Net) and updating the date of death in the routine data it was observed that 48.3% (95% CI: 44.4% – 52.3%) of the linked cases had defaulted based on clinic visit dates. Despite the biased selection of the study population (i.e., only considering deaths from HIV/AIDS), this is an extraordinarily high proportion of LTFU. Etoori *et al* 2020 attributed an unpublished analysis from TIER.Net by Pillay (25), revealing LTFU rates ranging from 11% to 15% in the first 3 months and from 27% to 34% in the first year of ART (26). We note that the average time since starting treatment for our study population was 46 months which may be a contributing factor to the high LTFU that was observed.

Determining the outcome status in routine clinical care of LTFU patients is often complicated and resource intensive. The lack of integrated medical record systems in many settings and complexity in tracing patients who do not return for scheduled visits results in patients being classified as LTFU even although this category is a combination of those who have disconnected from care, died, or who are receiving care elsewhere. Undocumented patient transfers among ART initiates continue to be an important potential source of misclassification when assessing retention in HIV care (6). Etoori *et al* 2020 identified TIER.Net misclassification by finding 40% of the deaths in their study were not captured and 43% were recorded as transferred out. Their study also found that patients recorded as LTFU in TIER.Net were more likely to be misclassified as deceased or transferred outpatients. Chammartin *et al* 2018 recommends that mortality in patients LTFU be taken into consideration for unbiased assessments of program outcomes (27). Fox *et al* 2010 (15) also recommended that it would be ideal for clinics to be linked to the death registry to determine the vital status of LTFU patients. Our study found that only 40.7% of the decedents (and not 100%) identified in TIER.Net were recorded as having died, illustrating the potential value of linking the routine programme data with a death register. Such a data linkage would need to be done using the South African Identity document (SA ID) number, suggesting that it would be ideal for the routine programme data to ensure the collection of correct SA ID number data or make use of the Health Patient Registration System (HPRS) (28) patient identifiers to enhance data linkage.

Our study revealed a poor level of agreement between the VA narratives and TIER.Net. The agreement is relatively high (59.1%) because it counts all matching cases, whether meaningful or random. However, the Kappa is low (0.17) because it adjusts for chance, only measuring true agreement beyond random matches. This means much of the observed agreement has arisen by chance, leading to a lower Kappa. The VA narratives lacked sensitivity in identifying treatment defaulters, although specificity was reasonably high. It remains uncertain whether

incorporating structured questions related to treatment default into the VA questionnaire would elicit such information, or if such details are simply unknown to NOKs due to the stigma and sensitivities surrounding HIV/AIDS in our context. A study by King et al in 2016 (29) reported that while VA narratives provided rich information on care-seeking, healthcare provision, and social factors leading up to death, they were not reliable for making diagnoses. Additionally, a study employing mixed methods to investigate VA narratives and circumstances of mortality (COM) indicators for assessing access and barriers to care for individuals who died of cardiovascular causes in a rural South African setting emphasized the necessity of strategies to improve care-seeking and receiving during the final illness (30). Further research is needed to explore whether COM indicators in VA could be expanded reliably to encompass information on treatment defaulting.

STUDY LIMITATIONS

Only 58.8% of the NCODV HIV cases were linked with data in TIER.Net, and of those, only 53.6% could be used for our analysis due to incomplete information about clinic visit dates. It is possible that this low proportion could have introduced potential bias. While younger age groups, females and selected provinces tended to be over-represented in the linked data, it is not clear how this would affect the findings. Since the unlinked/excluded cases had a lower default rate of 21.9%, it is possible that the poor performance of the VA narrative could be even worse. Furthermore, the evaluation of HIV information between the linked and unlinked/excluded cases revealed the possibility that some of the unlinked cases might not have had HIV. Nonetheless, we were able to achieve a required sample size for reasonable confidence intervals.

CONCLUSIONS

Although a high proportion of the VA narratives provided by NOKs about people who had died from HIV/AIDS suggested that the person had defaulted on their treatment prior to death, after linking the information about death with TIER.Net, it was found that almost half of the study population had defaulted on treatment. There is an urgent need to investigate reasons for the high level of defaulting. In addition, it would be ideal for routine programme data routinely include SA ID numbers to track LTFU patients through improved data linkage. The study found that information about treatment defaulting obtained from VA narratives was not accurate. Two-thirds of the defaulters were correctly identified and just over half of the non-defaulters were correctly identified. Further investigation into the possibility of including structured questions around defaulting in the VA might be useful.

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AUTHORS' CONTRIBUTIONS

M.M conceived and designed the study. M.M., N.N. and D.B., prepared data for analysis. M.M. conducted the literature review and drafted the manuscript. M.M., N.N. P.G, and interrogated and interpreted results. All authors critically reviewed the manuscript for important intellectual content and all authors approved the final version before submission.

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PART B: RESEARCH PROTOCOL

INTRODUCTION

Towards the end of 2018, the Joint United Nations Programme on AIDS estimated around 37.9 million people were infected with HIV worldwide and 28.2 million people have access to antiretroviral therapy (ART) (1). As of 2016, over 7 million South Africans are living with HIV of which 56% are receiving ART making this the largest ART programme in the world, which accounts for 20% of people on ART globally. A study review indicated that in South Africa between 2008 and 2013, only ± 67% of patients who initiated ART remained in care after 4 years and 40% of those who were lost to follow-up (LTFU) was attributed to known deaths (2).

High rates of LTFU have been reported in many HIV care and treatment programmes in sub-Saharan Africa (3). Patients who discontinued ART treatment are at high risk of illness and death because of AIDS-related conditions. Several studies have tried to quantify and determine the status of patients reported as LTFU, including several in South Africa (4). For example, in a large public hospital, it was determined that 31% of patients who defaulted soon after ART initiation had died, 25% had transferred and 44% had discontinued treatment voluntarily or could not be found (4). Another public sector clinic in South Africa showed similar results after tracing patients who were at least one month late for their last clinic visit 6 months after starting ART, where 41% had died, 7% had transferred, and 52% had voluntarily discontinued treatment or could not be found (5). Several methods have been used to obtain information on the vital status of LTFU patients, including patient tracing, the review of obituaries in newspapers and record linkage with civil registration and vital statistics (CRVS)(6, 7).

The CRVS system is well-established with a high proportion of deaths being registered in South Africa. However, the DNF is poorly completed by doctors and it impacts on the quality of cause-of-death information (8). The problem of underreporting and misclassification of HIV deaths has also been highlighted. The NCODV study assessed and validated the UCOD assigned on the death notification forms processed by Statistics South Africa (Stats SA) compared with information collected for a national sample of deaths. The preliminary results reported that 5,387 VA interviews were completed and 22.8% were identified as HIV/AIDS related deaths through the doctor reviewed VA, of which 10.2% of the VA narrative indicated that the decedent defaulted on their treatment (9).

South Africa has the largest ART programme in the world, but a few cohort studies of ART programmes have reported a high number of LTFU among patients who initiated ART in later years as compared to earlier years (3, 10). In 2018, an unpublished TIER.Net analysis showed that LTFU rates in the first 3 months were 11 to 15% compared to the 1st year which was 27% to 34% (11). The doctor reviewed VA HIV/AIDS related deaths will be linked in TIER.Net to confirm if the treatment default information provided by the VA narrative can be linked to the treatment outcomes in TIER.Net.

LITERATURE REVIEW

An insight into human immunodeficiency virus and acquired immunodeficiency syndrome epidemic in South Africa

South Africa holds the world's largest population of people living with human immunodeficiency virus (PLHIV), along with the highest number receiving antiretroviral therapy (ART) (12, 13). Since the 1990s, the country has witnessed a steady rise in HIV prevalence among pregnant women with rates reaching alarming levels by the early 2000s (14). Factors such as behavioural patterns, socioeconomic conditions and population mobility have fuelled the rapid spread of the virus (14). The government's response to the epidemic faced substantial criticism, particularly during the period from 1998 to 2008, marked by what was described as denialism (15). This lack of action led to the unnecessary loss of hundreds of thousands of lives due to the unavailability of ART (16). However, the introduction of the national rollout of ART in 2004 marked a significant shift in the approach to HIV/AIDS management (17).

Subsequent national strategic plans, such as the National Strategic Plan (NSP) for HIV and AIDS and sexually transmitted infections (STIs) (2007–2011), aimed to provide ART to a larger proportion of those in need, resulting in a substantial increase in the number of individuals receiving treatment (18). The adoption of the "Test and Treat" approach further accelerated the scale-up of ART, leading to millions of people being initiated on lifelong treatment. The Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets provided a framework for assessing progress in HIV/AIDS control efforts with South Africa making significant strides towards achieving these goals (19). Mathematical modelling studies have demonstrated the potential for achieving epidemic control by 2030 through the successful implementation of these targets (20, 21). However, challenges persist, particularly in monitoring and evaluating the effectiveness of ART programs. Issues such as loss to follow-up (LTFU), data reliability and monitoring adherence to treatment remain areas of concern.

The lack of standardized definitions and measurement methods for LTFU and retention in HIV/AIDS care poses significant challenges to assessing program effectiveness and patient outcomes. Different studies and programs use varying criteria and timeframes to define LTFU, leading to inconsistencies in reported rates and hindering meaningful comparisons (22, 23). Additionally, the absence of consensus on what constitutes successful retention further complicates efforts to evaluate interventions and improve patient outcomes (24, 25). These inconsistencies highlight the need for standardized definitions and measurement tools to accurately assess patient retention and guide programmatic interventions in HIV/AIDS care.

Misclassification of LTFU in HIV/AIDS care occurs when patients who are still engaged with care are incorrectly classified as being lost. This misclassification can lead to inaccurate assessments of program retention rates and hinder efforts to improve patient outcomes. Several studies have highlighted the prevalence of misclassification and its impact on program evaluation (26, 27). Factors contributing to misclassification include incomplete documentation, transfer of care between facilities and delays in updating patient records (27, 28). Addressing misclassification requires improved record-keeping practices, standardized definitions of LTFU and better tracking systems to accurately capture patient movements within the healthcare system (22, 27).

Overcoming HIV/AIDS data management challenges in resource-limited settings presents considerable hurdles, encompassing concerns about data quality, accuracy and accessibility. TIER.Net, an electronic patient registry,

emerges as a pivotal solution to these obstacles, facilitating comprehensive management of patient information, treatment data and program oversight. Research underscores the invaluable role of TIER.Net in addressing HIV/AIDS data management in resource-constrained environments. For instance, Mphatswe et al. (2012) demonstrated TIER.Net effectiveness in enhancing data completeness and timeliness, thereby fostering informed decision-making and optimizing resource allocation (29). Furthermore, TIER.Net has played a crucial role in bolstering the expansion of ART initiatives and monitoring patient progress.

However, despite its merits, TIER.Net faces challenges in comprehensively addressing misclassification issues (11). One such challenge arises from the variability in data entry practices and coding conventions across healthcare facilities, leading to inconsistencies in patient outcome classification. Additionally, reliance on passive data collection methods may contribute to underreporting of misclassified cases, particularly in settings with limited healthcare infrastructure and access. Moreover, the effectiveness of TIER.Net in mitigating misclassification depends on the availability of skilled personnel and resources for data validation and verification.

Introduction to verbal autopsy and its application

Verbal autopsy (VA) is a method used to collect information about the cause of death through interviews conducted by non-medical interviewers. Defined by the WHO as "a method used to ascertain the cause of a death based on an interview with next of kin or other caregivers", VA is particularly valuable in situations where deaths occur outside of medical facilities or in areas lacking robust vital registration systems (30). Originating in Asia and Africa during the 1950s and 1960s, researchers initially conducted physician interviews with relatives and caregivers to determine the cause of death, a method later named VA by workers in the Narangwal project in India (31, 32). The 1970s saw the WHO advocate for "lay reporting" by individuals lacking medical training, followed by the development of VA questionnaires in the late 1970s and early 1980s by Reproductive Age Mortality Studies in Bangladesh and Senegal (30, 33). However, concerns over instrument validity and data comparability arose in the early 1990s, leading to the establishment of expert committees to develop standardized VA tools, resulting in VA standards for maternal deaths in 1994 (34-36). In 2007, the WHO released three standard VA questionnaires for different age groups, aiming for certification and coding in alignment with the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (30).

Subsequent updates in 2012, 2014, and 2016 aimed to enhance cause-specific mortality data and ensure consistency and comparability across countries (32). Presently, VA typically involves two main stages: structured interviews with family members and caregivers of the deceased to gather information on signs, symptoms and medical history, followed by interpretation of interview data by physicians (Physician-Certified VA, [PCVA]) (30, 37) or automated methods (Computerised Coding of VA [CCVA]) such as InterVA and SmartVA, which utilize algorithms and probability theory (30, 38) to ascertain probable cause(s) of death. Data collection for VA often utilizes the Open Data Kit (ODK) software (39) on Android tablets, facilitating electronic data collection and translation of questionnaires, particularly useful in non-English speaking countries. Trained fieldworkers typically conduct interviews with close relatives or caregivers of the deceased at home, recording events preceding the death. An integral aspect of VA interviews is the inclusion of a free-text open narrative, designed to elicit the respondent's own account of the events leading to the death, complementing structured questions. The narrative aspect serves as a vital tool in capturing cultural beliefs and contextual nuances, aiding in the design of

interventions and services tailored to the needs of the community. Subsequently, a suspected cause of death is typically determined either through physician review or by applying statistical algorithms automatically, such as InterVA or SmartVA (33, 40, 41) .

VA also serves as a vital method for determining underlying causes of death (UCOD), typically validated against reference standards such as pathological autopsies, clinical records, or hospital medical records (MRs) in a process known as validation (42) . Chandramohan (2011) highlighted the importance of hospital diagnoses based on laboratory and clinical criteria as the most reliable gold standards for validating VAs (43). In the rural northeast region of South Africa, the Agincourt Health and Socio-Demographic Surveillance Site began using VA data in 1992 to assess HIV-related deaths, coinciding with the early stages of the HIV epidemic in the area (44). By 2005, approximately 70,000 individuals were documented, enabling a methodological exploration of the epidemic's progression through comparisons of physician-interpreted causes of death and probabilistically modelled causes of death (44).

Despite the global rollout of ART, the WHO VA questionnaire until 2012 only inquired about HIV status, but not about ART or tuberculosis treatment (38). Karat et al. (2018) conducted a study in South Africa to assess the sensitivity and specificity of the WHO 2012 VA questionnaire in detecting HIV status and ART initiation (45). They utilized clinical data, including clinic and hospital files to confirm HIV status and ART initiation, finding moderate to high sensitivity and specificity in identifying HIV status through the VA questionnaire. Additionally, a high proportion of ART initiation dates identified through VA were within three months of the confirmed date from clinical records (45). Another study conducted at the Karonga Health and Demographic Surveillance Site in Malawi compared VA data on HIV status and ART usage with actual test records and clinic reports. The study aimed to evaluate the accuracy and validity of HIV/ART information obtained through VA, finding a reliable match with other data sources (46). However, some researchers argue against relying solely on the validation of computer-coded or physician-coded VA methods and health facility records as true gold standards for cause of death determination. They propose complete diagnostic autopsy (CDA), which integrates macroscopic, microscopic and microbiologic data with clinical information, as the most accurate method (47). CDA is considered the gold standard for cause of death determination due to its comprehensive nature and ability to minimize errors inherent in health facility-derived information (47).

Despite its utility, VA encounters challenges in accurately diagnosing HIV/AIDS-related deaths and misclassification due to overlapping symptoms with other diseases. Future research should focus on refining VA methodologies for investigating HIV/AIDS-related mortality and treatment defaulting, including the development of standardized questionnaires and diagnostic algorithms specific to HIV/AIDS. Collaboration between VA researchers, HIV/AIDS experts and public health agencies is essential to ensure accurate interpretation and utilization of VA data in informing policies and programs. Efforts to integrate VA into routine surveillance systems and strengthen healthcare infrastructure in resource-limited settings are crucial for effectively monitoring and responding to the HIV/AIDS epidemic.

The importance of data linkage in health research

Data linkage plays a pivotal role in health research by allowing researchers to integrate and analyse data from various sources, leading to comprehensive insights and improved decision-making. It enables researchers to combine information from diverse sources such as electronic health records, administrative databases and registries. This integration creates opportunities for studying complex health issues, understanding disease patterns and evaluating healthcare interventions (48).

A review by Boyd et al. (2012)(49) highlights the role of data linkage in longitudinal studies aimed at understanding the long-term impact of health interventions and exposures. Longitudinal data linkage allows researchers to track individuals over time, assess changes in health status or behaviour and evaluate the effectiveness of interventions in real-world settings. By linking data from multiple time points, researchers can establish causal relationships, identify risk factors for disease and measure the effectiveness of public health interventions.

In addition to improving the quality and utility of health data, data linkage also holds promise for addressing health disparities and promoting health equity. A study by Goldstein et al. (2019)(50) explored the potential of data linkage in identifying and addressing disparities in healthcare access and outcomes among vulnerable populations. By linking data on social determinants of health, such as socioeconomic status, race/ethnicity and geographic location, researchers can identify disparities in health outcomes and inform targeted interventions to address underlying drivers of inequity.

Overall, the literature emphasises the importance of data linkage in advancing public health research, surveillance and policy. By integrating data from multiple sources and leveraging longitudinal and cross-sectional approaches, data linkage enables researchers to generate robust evidence, identify emerging health trends and inform decision-making aimed at improving population health and reducing health inequities. The advancements in data linkage methodologies offer promising avenues for comprehensive epidemiological assessments and program evaluations. By integrating diverse data sources, including VA narratives and treatment databases like TIER.Net, this study aims to elucidate the complex dynamics of HIV/AIDS and enhance the validity of mortality data.

AIMS AND OBJECTIVES

The aim of this sub-study is to assess whether the VA narrative can provide valid information about ART treatment default by linking the HIV/AIDS related death data from the NCODV with treatment information on TIER.Net. The National Department of Health (NDOH) supports a nationwide HIV treatment programme and has established the Three Integrated Electronic Registers (TIER.Net) to support HIV and antiretroviral ART monitoring. Once a patient with HIV is enrolled on the department's ART programme, their visits are recorded on TIER.Net including the provision of ART.

The specific objectives:

- What proportion of HIV/AIDS deaths identified by the VA interview mention “treatment default” in the narrative?
- What proportion of individuals who died from HIV/AIDS can be found in TIER.Net?
- Describe the characteristics used from the HIV/AIDS deaths to identify those found with those not found TIER.Net.
- Measure agreement between treatment default from the VA narrative and from TIER.Net.
- Measure sensitivity and specificity of identifying treatment default through the VA narrative.

METHODS

Study design

This descriptive study is based on the secondary analysis of data from the NCODV study which conducted VA interviews to identify causes of death of people that has been linked with data about ART treatment on TIER.Net, the national HIV treatment register.

Study population and sampling

The target population consist of 11 minors and 1,163 adult decedents (1,174) out of the 5,387 VA interviews from the NCODV that were certified by a doctor to have an UCOD of HIV/AIDS. The NCODV study included people who died between the of 1st September 2017 and 13th April 2018 in 27 randomly selected health sub-districts in South Africa.

Based on a specified margin of error for the estimates of a proportion, a sample size of 789 will be sufficient to estimate a population proportion with a 2% margin of error and 95% confidence level (https://www.calculator.net/sample-size-calculator.html.) Thus, the sample size of 1,174 cases is adequate for the first three objectives. However, it is anticipated that not all cases will be linked with TIER.Net. A sample size of 560 will be sufficient to estimate a population proportion with a 3% margin of error. Initial exploration of data linkage suggests that this sample size will be achievable.

Characteristics of the study population

The number of participants is 1,174 HIV/AIDS related deaths where the baseline demographic variables in sex, age was explored (Table 1).

Table 1: Socio-demographic data of the HIV/AIDS related deaths.

Characteristics	Total (n)	Percentage (%)
Sex		
Female	542	46%
Male	632	54%
Age groups		
12 – 24 yrs	50	4%
25 – 44 yrs	621	53%
45 – 64 yrs	412	35%
65+ yrs	91	8%

Inclusion and exclusion criteria

Only the adult VA reviewed deaths, certified by a doctor to have an UCOD of HIV/AIDS will be included in the study. The study excluded HIV/AIDS deaths of infants and children between the age 4 weeks and 11 years as well as the other VA reviewed deaths not certified with HIV/AIDS as an UCOD.

Data collection and measurement

This study used NCODV data collected during 1st and 2nd phase study design:

- The 1st phase of fieldwork was recruiting funeral undertakers and Department of Home Affairs offices to inform decedents' next of kin about the study and seek permission for the research team to contact them at a later stage.

- The 2nd phase is when the trained fieldworkers contacted the next of kin to schedule an appointment for a face-to-face VA interview using the three questionnaires of the WHO 2016 instruments (51), which was translated into nine official languages.

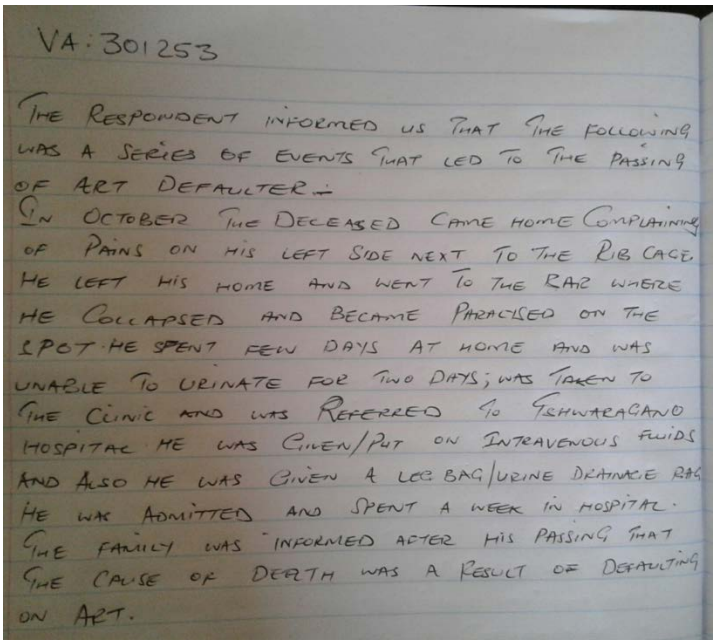
Identification of underlying cause of death

The NCODV study provided training to ensure that the doctors were competent in certifying the medical cause of death according to ICD-10 guidelines and were able to use the data capture tool as well as to understand the WHO 2016 VA tool and interpret the VA narrative and interview. The ICD-10 codes for the UCOD from doctor-certified and Iris coded VAs were run through the ANACONDA tool (52), to ensure that no biologically implausible causes had been assigned. Each doctor's VA record review form captured a short summary of the case, information on HIV and TB, the manner of death and the sequence of medical conditions leading to the death as would be reflected on a certificate of cause of death according to ICD-10 guidelines.

Identification of treatment default

Before the fieldworker administered the WHO VA questionnaire 2016 (51), the next of kin was probed to describe the context and symptoms preceding the death of the decedent. These details were captured in an unstructured (open) narrative section: "*Ask the respondent about the circumstances of the decedent's death. Capture in your notebook, before continuing with the interview. Keep in mind to make notes on the narrative throughout the questionnaire, where relevant. For specific questions, a reminder instruction will be displayed as part of the question. Probe for additional details on when respondent recognized symptoms, care sought, barriers to care, issues with transport, abnormalities, etc.*"

A picture was taken of the narrative by the fieldworker using ClearScanner and saved as a jpeg (see example in Figure 1).


VA: 301253

THE RESPONDENT INFORMED US THAT THE FOLLOWING WAS A SERIES OF EVENTS THAT LED TO THE PASSING OF ART DEFAULTER:-
IN OCTOBER THE DECEASED CAME HOME COMPLAINING OF PAINS ON HIS LEFT SIDE NEXT TO THE RIB CAGE. HE LEFT HIS HOME AND WENT TO THE BAR WHERE HE COLLAPSED AND BECAME PARALISED ON THE SPOT. HE SPENT FEW DAYS AT HOME AND WAS UNABLE TO URINATE FOR TWO DAYS; WAS TAKEN TO THE CLINIC AND WAS REFERRED TO GWANDAGANDO HOSPITAL HE WAS GIVEN/PUT ON INTRAVENOUS FLUIDS AND ALSO HE WAS GIVEN A LEG BAG/URINE DRAINAGE BAG HE WAS ADMITTED AND SPENT A WEEK IN HOSPITAL.
THE FAMILY WAS INFORMED AFTER HIS PASSING THAT THE CAUSE OF DEATH WAS A RESULT OF DEFAULTING ON ART.

Figure 1: An example of a VA narrative explaining the events leading to death.

The text from each narrative was transcribed into excel in the project office. Treatment default will be identified by reading the narratives. Keywords that clearly imply that the decedent had defaulted on treatment will be used to identify decedents that the next of kin reported had defaulted.

Some of the keywords identified in a pilot:

"Defaulting; defaulted; taking medication on and off; sometimes taking treatment; sometimes her defaulted; stop taking treatment; stopped taking ARV; refused to take the medication; refused and don't take anymore; didn't want to take treatment; was not taking his medication regularly; not taking her medication accordingly; he took his medication then later he stopped; stopped taking medication; He was taking his treatment properly for the first two years then he started to default thereafter; stopped drinking his treatment; was not consistent with her

ARVs; he was not drinking the treatment; Started defaulting; used to take treatment and defaulted; he started forgetting his medication and defaults; She stopped taking treatment and she defaulted; he wasn't taking his medication.

DATA MANAGEMENT AND ANALYSIS

In the doctor reviewed summary, treatment default was indicated for some and not all HIV/AIDS related deaths pending on the doctor. The VA narratives will be read to confirm and identify more cases. Table 2 was created based on the those identified to have defaulted in treatment by the doctor reviewed summary, the VA narrative and cases found or not from TIER.Net will be added.

Table 2: Variable list generated from the medical doctor review summary.

Variable	Description	Categorical
UniqueIDnew	Participant's number	Numerical (discreet)
Sex	Male or Female	Categorical (binary)
Age in years (yrs)	12 - 24 yrs 25 - 44 yrs 45 - 64 yrs	Categorical (ordinal)
Underlying cause of death (UCODFinal)	B20, B21, B22, B23, B24	Categorical (ordinal)
Did the Drs summary indicate treatment default?	Yes/No	Categorical (binary)
Did the narrative indicate treatment default?	Yes/No	Categorical (binary)
Was the decedent found in TIER.Net?	Yes/No	Categorical (binary)

DATA LINKAGE

Decedent's personal information taken from the doctor reviewed summary will be collated and shared in a password protected Excel spreadsheet with the official in the National Department of Health who managed the Three Integrated Electronic Registers (TIER.Net) for linkage and to return an anonymised analysis data set for the study (Table 3).

Table 3: Description of variable used to link in TIER.Net**.**

Variable	Description	Categorical
UniqueIDnew	Participant's number	Numerical (discreet)
Sex	Male or Female	Categorical (binary)
Name, Other name and Surname	Names and surname	Categorical (nominal)
Date of Birth	Date	Categorical (ordinal)

Variable	Description	Categorical
ID Number	RSA 13-digit number	Categorical (ordinal)
Place of residence	Address	Categorical (ordinal)
Province of Death	Province name	Categorical (nominal)

- TIER.Net is a 3-Tiered approach which provides the tools to support the ART monitoring. The following sections were requested:
- ART – Day started treatment, transfer in location etc.
- Outcomes – Transfer or moved out and LTFU.
- Treatment Visits – date of visit and when stopped attending clinic.

DATA ANALYSIS

Measurement

The main outcome of interest is treatment defaulting identified from the VA narrative, as specified in Table 2. This binary variable will be used to determine the proportions of how many HIV/AIDS related deaths indicated treatment default. It will be compared with the mention of treatment default in the medical summary of the VA by the doctor reviewer. Treatment default indicators in TIER.Net are Last ART visit date (last visit date when the patient seen at a facility) and code (last regimen given). The outcome characteristics like LTFU, Transferred/Moved Out or Died are indicators if a patient is still attending clinic or not. Last ART treatment date will be subtracted with the date of death to determine when last the patient was seen at a clinic. Sensitivity and specificity approaches will be used to assess agreement between treatment default from the VA narrative and TIER.Net, the main purpose of the study. Statistical significance for all analyses will be evaluated using 95% Confidence Intervals (CI) and an α-level of 0.05. Cohen's kappa coefficient will also be used to measure low, medium and high levels of agreement. Data will be analysed using the STATA 15.1 software.

Study limitation

The VA is not the highest level of evidence, forensic autopsy and medical records are but do not have access. The VA UCOD is validated in TIER.Net. The study recognises that TIER.Net might not have reliable ID numbers.

ETHICAL AND LEGAL CONSIDERATIONS

Permissions

The NCODV study sort permission from the national, provincial and district health departments as well as individual facilities to access information of decedents from medical and forensic records at public hospitals and forensic autopsy facilities. Permission to access forensic pathology records in KwaZulu Natal could not be secured. The protocol was presented to the National Forensic Pathology Services Committee to obtain their support.

Description of risks and benefits

This study is an analysis of secondary data generated from the main study (NCODV) and no direct risks are involved. The benefit of having the treatment default question in the VA questionnaire could assist in identifying more of such cases as revealed in the narrative. This could be of great benefit to policy makers of this country.

Informed consent process

The main study (NCODV) under the Burden of Disease Research unit was provided ethical clearance approval by the SAMRC Ethics Committee where informed consent procedures were followed. However, this study will be requesting ethical approval from the University of Cape Town Human Research Ethics Committee (UCT-HREC). Informed consent will not be obtained from participants.

Privacy and Confidentiality

To ensure privacy and confidentiality, unique identity numbers were provided for each participant by the NCODV study. All identifiable personal information was stored in a password protected Excel spreadsheet. Only the principal investigator and research team members have access to these data. The final anonymized dataset will be archived and stored with metadata for 20 years in a data repository at the SAMRC.

Reimbursement for Participation

Not applicable to this study, this study is using secondary data for analysis.

Emergency Care and Insurance for Research-related Injury

Not applicable to this study, this study is using secondary data for analysis.

Budget

The researcher is funded by the SAMRC Intra-Mural Post- Doctoral Fellowship Programme. The data management and analysis will be done by the researcher and biostatistical guidance will be obtained from the SAMRC Biostatistics Unit.

What Happens at the End of a Study?

At the end study, a mini dissertation in partial fulfilment of the requirements for a Master of Public Health degree at the University of Cape Town will be submitted. A manuscript will be prepared for submission in a relevant peer-reviewed journal.

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PART A: RESEARCH APPENDICES

TABLES AND FIGURES

Annexure 1

Phrases discovered in the narratives implying treatment defaulting:

Defaulting; defaulted; taking medication on and off; sometimes taking treatment; sometimes her defaulted; stop taking treatment; stop drinking tablets; refused to take medication; started refusing to take medication; not taking medication properly; started taking ARVs in mid-2013 and stopped again; not taking his HIV treatment correctly; not taking treatment; stopped taking ARV; refused to take the medication; refused and don't take anymore; didn't want to take treatment; was not taking his medication regularly; not taking her medication accordingly; he took his medication then later he stopped; stopped taking medication; He was taking his treatment properly for the first two years then he started to default thereafter; refused to take his medication; stopped drinking his treatment; sometime skips to fetch her medication; was not consistent with her ARVs; not taking treatment well; he was not drinking the treatment; Started defaulting; used to take treatment and defaulted; he started forgetting his medication and defaults; she no longer took treatment for HIV; She stopped taking treatment and she defaulted; he wasn't taking his medication; She was taking her medication not properly because sometimes she would jump days without taking medication; didn't take ARVs according to a schedule; She took her medication but relapse last year; She used skip taking tablets.

Figure 1: Examples of last clinic visit date (LastARTVisitDate) captured after the date of death.

UniqueIDnew	Dateofdeath	StartedARTDate	LastARTVisitDate	LastARTVisitCode	Outcome	OutcomeDate	Comment
202064	2017-09-09	2016-07-01	2018-01-04	1TFE	RIP	2018-01-29	LastARTvisit after DOD
401363	2018-03-24	2016-03-07	2018-05-09	1TFE	RIP	2018-07-05	LastARTvisit after DOD
501264	2018-04-08	2011-11-17	2019-05-31	Did Not Attend	RIP	2019-09-26	LastARTvisit after DOD
502114	2018-02-02	2018-02-15	2018-02-15	1TFE	RIP	2018-03-02	LastARTvisit after DOD
503032	2018-02-06	2017-10-23	2018-02-23	1TFE	RIP	2018-06-07	LastARTvisit after DOD
601018	2018-03-31	2015-01-21	2018-11-06	Did Not Attend	RIP	2018-11-06	LastARTvisit after DOD
602120	2018-01-29	2015-08-28	2018-04-04	1TFE	RIP	2018-04-04	LastARTvisit after DOD
602161	2018-01-23	2014-07-23	2018-01-26	1A3E	RIP	2018-03-29	LastARTvisit after DOD
602208	2018-03-03	2017-11-21	2018-03-16	1TFE	RIP	2018-03-19	LastARTvisit after DOD
901104	2018-03-01	2009-12-02	2019-01-15	Did Not Attend	RIP	2019-01-15	LastARTvisit after DOD
902249	2018-03-23	2017-10-09	2018-04-06	1TFE	RIP	2018-04-09	LastARTvisit after DOD

Table 1: Sample sizes to estimate a population proportion of 50% with specified error margin at 95% CI level.

Margin of error	Sample size
2%	789
3%	**560**
4%	398
5%	290

Figure 2: Excluded sixty-two cases with missing dates, outcomes and date of death captured after last clinic visit.

UniqueIDnew	Dateofdeath	StartedARTDate	LastARTVisitDate	LastARTVisitCode	Outcome	OutcomeDate
102032	2018-02-27	No dates	No dates	No dates	LTF	2015-09-01
103012	2018-01-25	No dates	No dates	No dates	RIP	2018-01-25
201051	2018-03-15	No dates	No dates	No dates	RIP	2018-03-16
201122	2018-03-01	No dates	No dates	No dates	No outcome	No dates
202277	2017-09-15	No dates	No dates	No dates	No outcome	No dates
203082	2017-11-20	2013-02-28	2018-07-11	Did Not Attend	LTF	2018-07-11
303266	2017-11-16	No dates	No dates	No dates	LTF	2020-12-28
401106	2017-11-22	No dates	No dates	No dates	LTF	2017-04-04
401363	2018-03-24	2016-03-07	2018-05-09	1TFE	RIP	2018-07-05
401520	2018-04-06	No dates	No dates	No dates	TMO	2017-08-10
401572	2018-04-11	No dates	No dates	No dates	LTF	2018-04-11
401757	2018-01-01	2003-12-25	2018-01-10	1TFE	RIP	2018-01-10
401770	2018-02-04	No dates	No dates	No dates	LTF	2017-11-03
402071	2017-09-18	No dates	No dates	No dates	No outcome	No dates
402077	2017-09-13	No dates	No dates	No dates	RIP	2017-09-14
402091	2017-11-17	No dates	No dates	No dates	TMO	2017-10-13
403016	2018-03-19	No dates	No dates	No dates	TMO	2013-11-30
403035	2018-03-18	No dates	No dates	No dates	No outcome	No dates
403037	2018-04-12	No dates	No dates	No dates	No outcome	No dates
403222	2018-02-27	No dates	No dates	No dates	LTF	2019-05-06
501052	2018-03-14	No dates	No dates	No dates	No outcome	No dates
501076	2017-11-12	No dates	No dates	No dates	No outcome	No dates
501112	2018-04-01	No dates	No dates	No dates	No outcome	No dates
501182	2018-04-11	No dates	No dates	No dates	No outcome	No dates
501247	2018-12-06	No dates	No dates	No dates	LTF	2018-06-05
501251	2018-03-08	No dates	No dates	No dates	RIP	2018-03-08
501264	2018-04-08	2011-11-17	2019-05-31	Did Not Attend	RIP	2019-09-26
501294	2018-02-11	No dates	No dates	No dates	RIP	2018-02-14
501341	2018-03-29	No dates	No dates	No dates	No outcome	No dates
501388	2018-02-21	2020-01-20	2020-01-20	1TFE	LTF	2020-01-21
501437	2018-03-26	No dates	No dates	No dates	No outcome	No dates
501441	2018-04-04	No dates	No dates	No dates	No outcome	No dates
501531	2018-02-06	No dates	No dates	No dates	RIP	2018-01-10
501537	2018-02-22	No dates	No dates	No dates	No outcome	No dates
502114	2018-02-02	No dates	No dates	No dates	TMO	2018-02-28
502119	2018-03-03	No dates	No dates	No dates	TMO	2020-04-22
502238	2018-03-11	No dates	No dates	No dates	No outcome	No dates
502291	2018-02-04	No dates	No dates	No dates	No outcome	No dates
601027	2018-03-21	2016-11-03	2018-05-30	Did Not Attend	LTF	2018-05-30
602031	2018-01-09	No dates	No dates	No dates	TMO	2017-12-05
602066	2017-11-18	2013-09-20	2017-12-14	Did Not Attend	LTF	2017-12-14
602161	2018-01-23	2014-07-23	2018-01-26	1A3E	RIP	2018-03-29
603200	2018-04-05	No dates	No dates	No dates	LTF	2019-09-16
603339	2017-12-11	No dates	No dates	No dates	RIP	2017-12-11
701177	2018-03-06	No dates	No dates	No dates	TMO	2018-02-28
703027	2018-03-17	No dates	No dates	No dates	LTF	2017-10-04
703170	2018-04-08	No dates	No dates	No dates	LTF	2018-03-01
801002	2017-11-19	2015-06-22	2021-07-01	1TFE	No outcome	No dates
801173	2018-03-14	2018-02-06	2018-04-04	Did Not Attend	LTF	2018-04-04
801213	2018-03-22	No dates	No dates	No dates	No outcome	No dates
801285	2017-12-10	2010-06-10	2018-04-04	1TFE	LTF	2018-04-04
801328	2018-03-18	No dates	No dates	No dates	No outcome	No dates
803095	2018-04-07	2016-10-26	2018-05-15	Did Not Attend	LTF	2018-05-15
803107	2018-03-19	No dates	No dates	No dates	TMO	2018-03-08
803113	2017-12-21	No dates	No dates	No dates	LTF	2017-11-29
803126	2018-03-19	No dates	No dates	No dates	No outcome	No dates
803156	2018-04-02	No dates	No dates	No dates	No outcome	No dates
803159	2018-04-04	2017-09-12	2018-04-10	Did Not Attend	LTF	2018-04-10
803165	2017-11-14	2012-04-12	2018-02-16	Did Not Attend	LTF	2018-02-16
901017	2018-03-27	No dates	No dates	No dates	No outcome	No dates
901104	2018-03-01	2009-12-02	2019-01-15	Did Not Attend	RIP	2019-01-15
902232	2018-03-14	No dates	No dates	No dates	RIP	2018-01-29

Table 2: WHO 2016 VA questionnaire and Doctor's VA review summary HIV/AIDS related information by TIER.Net linking status.

Characteristics	Total 1 174 (100.0%)	Linking status		
		Included (linked) 629 (100%)	Excluded 545 (100%)	p-value
WHO 2016 VA questionnaire				
Was an HIV test ever positive?				<0.001
Yes	1 024 (87.2%)	582 (92.5%)	442 (81.1%)	
No	90 (7.7%)	22 (3.5%)	68 (12.5%)	
Doesn't know	60 (5.1%)	25 (4.0%)	35 (6.4%)	

Characteristics	Total 1 174 (100.0%)	Linking status		
		Included (linked) 629 (100%)	Excluded 545 (100%)	p-value
Was there any diagnosis by a health professional of AIDS?				0.006
Yes	524 (44.6%)	306 (48.6%)	218 (40.0%)	
No	549 (46.8%)	266 (42.3%)	283 (51.9%)	
Doesn't know	100 (8.5%)	57 (9.1%)	43 (7.9%)	
Refused to answer	1 (0.1%)	0 (0.0)	1 (0.2%)	
Did (s)he receive (or need) antiretroviral therapy (ART)?				0.001
Yes	538 (45.8%)	320 (50.9%)	218 (40.0%)	
No	283 (24.1%)	131 (20.8%)	152 (27.9%)	
Doesn't know	353 (30.1%)	178 (28.3%)	175 (32.1%)	
Physician review of VA				
HIV status				<0.001
Positive	1 057 (90.0%)	594 (94.4%)	463 (84.9%)	
HIV status not reported but on ARV treatment (not PMTCT)	14 (1.2%)	6 (0.9%)	8 (1.5%)	
Symptoms and signs suggestive of HIV despite HIV status reported as negative or unknown	103 (8.8%)	29 (4.6%)	74 (13.6%)	
HIV/AIDS definite				<0.001
HIV positive	1 075 (91.6%)	602 (95.7%)	473 (86.8%)	
No indication of HIV	99 (8.4%)	27 (4.3%)	72 (13.2%)	

Table 3: TIER.Net clinical outcomes.

```
. tab Outcome
```

Outcome	Freq.	Percent	Cum.
LTF	254	40.38	40.38
RIP	256	40.70	81.08
TMO	115	18.28	99.36
Unknown	4	0.64	100.00
Total	629	100.00	

Figure 3: Level of agreement between the VA narratives and TIER.Net.

```
. kap did newCon

             Expected
Agreement    Agreement     Kappa   Std. Err.         Z      Prob>Z
------------------------------------------------------------------
  59.14%      50.69%     0.1714     0.0368       4.66      0.0000

. kapci did newCon

                                          N=629
------------------------------------------------------------
 Kappa (95% CI) = 0.171 (0.100 - 0.243)    (A)
------------------------------------------------------------
 A = analytical
```

Figure 4: Sensitivity and specificity analysis.

```
. diagtest Didthenarrativeindicatetreat Condition

   Did the |
 narrative |
  indicate |
 treatment |       Condition
  default? | Treatment  Treatme..  |     Total
-----------+-----------------------+----------
        No |       256        188  |       444
       Yes |        69        116  |       185
-----------+-----------------------+----------
     Total |       325        304  |       629

True D defined as Condition ~= .                      [95% Conf. Inter.]
------------------------------------------------------------------------
Sensitivity                     Pr( +| D)  38.16%      34.36%   41.95%
Specificity                     Pr( -|~D)  78.77%      75.57%   81.97%
Positive predictive value       Pr( D| +)  62.70%      58.92%   66.48%
Negative predictive value       Pr(~D| -)  57.66%      53.80%   61.52%
------------------------------------------------------------------------
Prevalence                      Pr(D)      48.33%      44.43%   52.24%
------------------------------------------------------------------------

.
```

PART B: PROTOCOL APPENDICES

Annexure 2 – Ethics Approval letter(s)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 August 2022

HREC REF: 346/2022

Prof L Myer
Division of Epidemiology & Biostatistics
FHS
Email: Landon.myer@uct.ac.za
Student:MqnMon001@myuct.ac.za

Dear Prof Myer

PROJECT TITLE : DOES A VERBAL AUTOPSY NARRATIVE PROVIDE ACCURATE INFORMATION ABOUT TREATMENT DEFAULT FOR PEOPLE WHO HAVE DIED FROM HIV/AIDS?- (MASTERS CANDIDATE-DR MONIQUE MAQUNGO)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Monique Maqungo will also be involved in this study

Please quote the HREC REF 346/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HUMAN RESEARCH ETHICS COMMITTEE
14 JUL 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.8.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	16/7/2023

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14 July 2023		
HREC REF Number	346/2022	Current Ethics Approval was granted until	30 August 2023
Protocol title	Does a verbal autopsy narrative provide accurate information about treatment default for people who have died from HIV/AIDS?		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☐ No ✔	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Landon Myer		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Department / Office Internal Mail Address	Epidemiology and Biostatistics Landon.Meyer@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐ No✓
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No✓

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐✓
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2:

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Contact person	
Telephone number	
Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

Protocol
Ethics approval letter

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐✓	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	1 174
Number of participants enrolled, since last HREC Progress report (continuing review)	1 174
Additional number of participants still required	N/A

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	N/A

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

6. Cumulative summary of participants

Total number of participants who provided consent	1 174
Number of participants determined to be ineligible (i.e. after screening)	N/A
Number of participants currently active on the study	N/A
Number of participants completed study (without events leading to withdrawal)	N/A
Number of participants withdrawn at participants' request (i.e. changed their mind)	N/A
Number of participants withdrawn by PI due to toxicity or adverse events	N/A
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	N/A
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	N/A
Participants are all deceased.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	
N/A	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Data linkage was successful for 691 (58.9%) deaths but 62 (5.3%) could not be analysed due to inconsistent information and 41.1% did not link in TIER.Net. Data analysis has been completed and currently completing first draft of the mini thesis (article format). Briefly, the study findings showed almost half (48.3%) of the 629 analysed cases were identified as treatment defaulters in TIER.Net compared to 29.4% from the VA narratives. Overall agreement between VA narratives and TIER.Net was 59.1% with a kappa value of 0.17 (95% CI: 0.10 – 0.24). The sensitivity and specificity of the VA narratives for identifying treatment defaulters were 38.2% (95% CI: 34.4 – 42.0) and 78.8% (95% CI: 75.6 – 82.0) respectively with positive and negative predictive values of 62.7% (95% CI: 58.9 – 66.5) and 57.7% (95% CI: 53.8 – 61.5), respectively.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐✓	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☐ Not applicable ✓
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No ✓	☐ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No ✓	☐ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

	DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☐ No✓
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
N/A

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**		
☐ Yes	☐ No	☐ Not Applicable – N/A✓
If yes, please complete the following:		
Insurer's name:		
Policy no.	*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.		

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☐ No ✓
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	14.07.2023

THE INSTRUCTIONS FOR AUTHORS FOR GLOBAL HEALTH ACTION

Annexure 3: Manuscript Submission Guidelines

(Revised December 2023)

Initial Submission

Manuscript Submission Guidelines

Original Research articles - up to 4000 to 6000 words: An Original Research article must follow the following structure: Background, Methods, Results, Discussion and Conclusions. *Global Health Action* publishes articles based on quantitative and/or qualitative designs, and authors should follow the relevant reporting guidelines.

Reporting Guidelines

- For observational studies, please follow the STROBE guidelines

STROBE Statement—checklist of items that should be included in reports of observational studies.

	Item No	Recommendation	Page No	Comments
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract.	2-3	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found.	2-3	✓
			Introduction	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.	4	✓
Objectives	3	State specific objectives, including any prespecified hypotheses.	4	✓
			Methods	
Study design	4	Present key elements of study design early in the paper	5	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	5	✓
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment	5	✓ Cross-sectional study ✓ Created a flow diagram to describe the

		and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants.		eligibility criteria.
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed. Case-control study—For matched studies, give matching criteria and the number of controls per case.		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5	✓ Treatment defaulting has been defined as primary outcome for both VA narratives and for TIER.Net.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	5-7	✓ Data sources described.
Bias	9	Describe any efforts to address potential sources of bias		✓ Potential bias is described under study limitations.
Study size	10	Explain how the study size was arrived at	7	✓ Study size described.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why?		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding.	7	
		(b) Describe any methods used to examine subgroups and interactions.		✓
		(c) Explain how missing data were addressed		✓ Missing data excluded.

		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		✓
		(e) Describe any sensitivity analyses		
Results				
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	✓
		(b) Give reasons for non-participation at each stage	8	✓
		(c) Consider use of a flow diagram	8	✓ Flow diagram described in method section.
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders.	9	✓
		(b) Indicate number of participants with missing data for each variable of interest.	9	✓
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time.		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure.		
		Cross-sectional study—Report numbers of outcome events or summary measures.		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10	✓

		(*b*) Report category boundaries when continuous variables were categorized.		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.		
Discussion				
Key results	18	Summarise key results with reference to study objectives.	11	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results.		
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	12	✓

Manuscript Guidelines

Manuscript length: Global Health Action has no strict upper limit for manuscript length but authors are advised to follow the recommendations given here for different types of articles. The word limits exclude references, tables and figures. Over-long manuscripts are likely to be rejected or returned for major revisions.

Acronyms: Acronyms, or short abbreviations, should only be used if the term is repeated more than three times throughout the manuscript. Define the full term at first use (with the abbreviation adjacent in parentheses). Use consistently thereafter. Do not use acronyms in the title, abstract, sub-headings or Paper Context section unless the abbreviation is well known and commonly used in global health. Do not start a sentence with an acronym. Do not use acronyms for organisations that are cited as authors of reports in the reference list (e.g., World Health Organization rather than WHO, United Nations rather than UN).

Manuscript format: Manuscripts must be prepared using Microsoft Word. Use double spacing and font size 11 or 12 point. Include page numbers at the bottom of the page and add line numbers to the entire document. (Click continuous). Do not number section headings.

Figures and tables can be placed either within the text or submitted as separate documents. Figures should be of sufficient resolution to enable evaluation.

1. All manuscripts must include the essential elements needed to evaluate a manuscript: abstract, author affiliations, figures, tables, funder information, and references. Further details may be requested upon acceptance.

2. References should be in **NLM style or format**. If there are more than six authors list the first six followed by et. al. Otherwise list all authors and initials. Author name(s), journal or book title, article or chapter title, year of publication, volume and issue (where appropriate) and page numbers are essential. All bibliographic entries must contain a corresponding in-text citation. The addition of DOI (Digital Object Identifier) where available is required. Organisation names should be spelled in full. (See previous section on acronyms). All cited references must be in English.

3. Spelling can be United States or United Kingdom English as long the use is consistent. Spell out numbers under 10 (zero through nine) and use the numeric symbols for numbers 10 and up.

4. Regardless of the file format in the original submission, an editable version of the article must be supplied during the revision stage. 4.5 Footnotes are accepted in this journal.

Title page: Reviewers see the title page and author details. Organize the title page in the following way: 1) title of manuscript; 2) name of author(s); 3) affiliations for all authors, including name of institution(s) and department(s); 4) email addresses of all authors, and 5) name and full postal address of the corresponding author who also acts as 'guarantor' for all parts of the manuscript. If published, the corresponding author's institution, postal and email addresses are displayed in the article PDF and the online version. The submitting author must also enter names and contact information for all coauthors during the submission process.

Effective titles are concise, accurate and informative. They should tell readers what the article is about and ‘trigger’ their interest to read more. Incorporate key words into the title to help ensure that the article will be found in online searches. Writing the title and abstract for your article - Author Services (taylorandfrancis.com)

The title page should also include a separate word count of the abstract and manuscript (excluding references, tables and figures). Include five to ten keywords or subjects that can be used for searching and retrieval. Remember that words already in the title will be automatically indexed. Think of other relevant keywords. Writing the title and abstract for your article - Author Services (taylorandfrancis.com)

Abstract: In writing the abstract focus on what the research is about, what methods were used and what was found out. Writing the title and abstract for your article - Author Services (taylorandfrancis.com) Articles in Global Health Action must include an abstract of no more than 250 words. The abstract should provide sufficient information for readers to be able to

decide whether or not to proceed to the full text. The abstract should not include sentences cut and pasted from the manuscript and acronyms should be avoided if possible. In some cases it may be necessary to use acronyms to keep within the word limit. Editors will make this judgement.

Structured abstracts with the headings: Background, Objective(s), Methods, Results, and Conclusions **(maximum 250 words)** are required for Research and PhD Synthesis articles.

Unstructured abstracts **(maximum 250 words)** are required for the following article types: Review, Methods Forum, Study Design, Capacity Building, Current Debate, and Short Communication.

You can opt to include a video abstract with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.

Manuscript sections: Research and review articles should follow the layout: Background, Methods, Results, Discussion, and Conclusion. Other types of articles may have different structures. See also Ethics and consent.

Section headings: Do not number section headings. Use a maximum of three levels of headings made clear by orthographic indicators, e.g., capitals, italics, bold, etc. Insert running page numbers in the footer.

Units and equations: Use SI units (non-italicized). If you are submitting your manuscript as a Microsoft Word document, ensure that all equations are editable. See here for more information about mathematical symbols and equations.

Tables: Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. The text should not labour the details in the tables. Ensure that all tables have been formatted correctly and are editable. Tables should have titles, column/row headings, and footnotes if applicable. Ensure that all parts of the tables fit within the page margins. If necessary, split large tables into two or more, but ensure column/row headings are provided on each page. Very large tables may be better presented as online supplementary material. Authors are encouraged to use one decimal point for percentages, and three decimal places for p values. The p is lowercase and italicized, and there is no hyphen between p and value. Note also that p=0.000 is not acceptable; instead write p<0.001. When writing numbers less than one use a zero before the decimal marker which should be a dot, not a comma. Figures: If the manuscript is accepted for publication, supply editable figures/graphics/images in at least 300 dpi files. Figures should be saved as TIFF, PostScript or EPS files. All charts (bar, pie, column, etc.) should be two dimensional, unless three dimensions are required to present the data. Online versions of articles normally include figures in colour, but some readers may use monochrome printed versions so check that important details do not disappear in monochrome. See more information on how to prepare artwork. If the figures/graphics/images have been taken from sources not copyrighted by the author, it is the author's sole responsibility to secure the rights from the copyright holder to reproduce those figures/graphs/images for both worldwide print and web publication. All reproduction costs charged by the copyright holder

must be borne by the author. When figures/graphics/images are reproduced, a parenthesis should be added to the figure legend thus: (Reproduced with permission from xxxx.)

End materials: Please supply end material information before the reference list and in the following order: Acknowledgments, Author Contributions, Disclosure Statement, Ethics and Consent, Funding Information, Paper Context and ORCID identifiers. If relevant authors will be asked to also supply statements on Data Availability and Data Deposition. If the article is a PhD Synthesis, authors must also add a further paragraph under End Materials titled 'Academic Details'. If the article is on a preprint platform, give details under the heading 'Preprints.'

See below for further details about the information required under each of these headings. Please provide in the order listed below.

Acknowledgements: All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support. Financial and material support should also be acknowledged. If authors have used artificial intelligence (AI) tools then this must be acknowledged and authors must declare the parts or sections of the paper in which AI was used. AI tools must not be listed as authors.

Author contributions: Global Health Action requires its authors to comply with authorship criteria as defined by the International Committee of Medical Journal Editors (ICMJE) in its requirements for authorship. The contributions of each author (using initials as appropriate) should be stated clearly and will be published in the article.

Disclosure statement: Authors are responsible for disclosing financial support from industry or other conflicts of interest that might bias the interpretation of results. This does not include salaries paid to authors by institutions with which the authors are affiliated. If you have no interests to declare, please state: The authors report no conflicts of interest. Read more on declaring conflicts of interest here. When manuscripts are accepted authors will be asked to complete the ICJME Competing Interests form.

Ethics and consent: Studies involving human participants, human material, or human data, must be performed in accordance with the Declaration of Helsinki. Researchers normally have to apply to an appropriate ethics committee for approval to conduct their study. Global Health Action requires authors to prepare a statement to this effect. The statement must include the name of the ethics committee, reference number and other relevant information. If the study has been granted an exemption from requiring formal ethics approval, this must be explained giving the name of the ethics committee that granted the exclusion. Some other studies do not require formal ethics approval and where this is the case, this must also be clearly explained and justified. Authors must be prepared to provide further information on the above to Global Health Action editors if so requested.

Where appropriate, a paragraph on ethics approval must be included in the Methods section.

Global Health Action reserves the right to reject any manuscript if the Editor considers that the research does not uphold high ethical standards and has not been carried out within an appropriate ethical framework.

Ethical considerations and measures taken to handle specific challenges in the research should be included as part of the method or discussion sections in the manuscript.

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