

“Which factors can be associated with loss to follow-up in the context of rural South Africa”

Thesis Based on Existing Data: Social Policy and Public Health (201800155)

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Abstract

Background: The human immunodeficiency virus (HIV) is a major health issue in South Africa. Treatment success requires that HIV infected people remain on treatment and are followed up regularly. Using a socioecological approach, this study investigated a wide range of factors that could be associated with being lost to follow-up (LTFU) in rural South Africa.

Methods: Data from the ITREMA randomised control trial (RCT) conducted at the Ndlovu clinic in Elandsdoorn, Limpopo, rural South Africa were used to assess which factors could be associated with LTFU. LTFU was defined as a participant who had not visited the clinic for more than 90 days after the last scheduled clinical visit date, and prior to end of study, without being transferred out or being documented as deceased. Through logistic regression, LTFU was analysed with the following potential covariates: sociodemographic, risk behaviour, depression, coping abilities, health literacy, physical health, adherence, social support, caregiver trust, stigma and quality of life.

Results: Out of 501 patients, 15.8% (n=79) were LTFU. Factors associated with LTFU included young age (odds ratio [OR]: 0.91, confidence interval [CI]: 0.86-0.96), depressive symptoms (OR: 11.32, CI: 2.44-61.58), low developed emotional orientated coping styles (OR: 0.84, CI: 0.73-0.95), high developed avoidance orientated coping styles (OR: 1.14, CI: 1.03-1.27), poor adherence (OR: 6.82, CI: 2.31-22.64) and a lower quality of life (OR:0.90, CI: 0.85-0.96).

Conclusion: Based on the results it is recommended that the South African government encourages healthcare providers to monitor the overall well-being of HIV infected individuals by screening for depressive symptoms and poor adherence and provides additional support to develop coping styles of HIV positive people to prevent low retention rates and achieve long-term treatment success. However, further research is recommended as not enough data on factors associated with LTFU is available.

Introduction

The Human Immunodeficiency Virus (HIV) epidemic is a major global health issue; approximately 36.9 million people lived with HIV by the end of 2017 (World Health Organization [WHO], 2018). The African region accounts for two thirds of these global HIV infections (WHO, 2018). In this region, South Africa has the highest absolute number of HIV infections globally with 7.2 million, about 12.8% of the total (UNAIDS, 2019). South Africa also has the highest rate of new infections with an estimated 270,000 new cases in 2016 (UNAIDS, 2019). The HIV epidemic in South Africa can be mainly found in rural, resource limited settings. In 2012 HIV prevalence was around 5% in urban settings compared to 17% in rural settings (Shisana, Rehle, et al., 2014). The South African government recognises the seriousness of the HIV epidemic and they have, in accordance with WHO guidelines, implemented a policy of treatment with antiretroviral therapy (ART) for all HIV-infected patients, irrespective of disease stage, starting in September 2016 (Republic of South Africa Department of Health, 2016; WHO, 2015). UNAIDS (2019) estimated that, in 2017, 61% of people who are HIV positive received ART in South Africa.

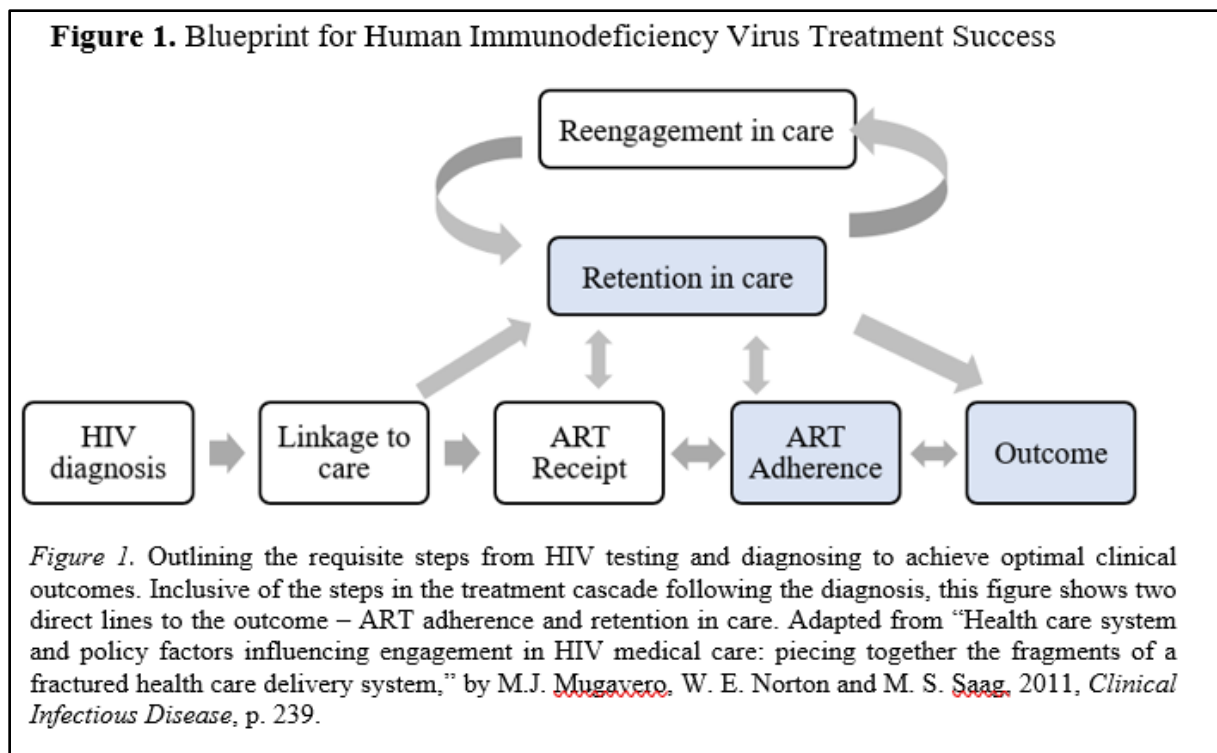
With this policy of universal treatment, South African HIV-infected individuals can have the same life expectancy as non-infected people (Clayson et al., 2006). However, for ART to be effective connection to clinical care and strict adherence is essential. Adherence can be described as the extent to which a patient follows the treatment plan as agreed upon with the healthcare professionals to get the desired results (Dracup & Meleis, 1982). Sufficiently high levels of adherence of 95% are crucial for viral suppression, preventing disease progression and death (Paterson et al., 2000). Nevertheless, HIV positive people do not always succeed in achieving or maintaining these high levels of adherence (Ortego et al., 2011). In 2017 it was estimated that in South Africa 38% of the people living with HIV and receiving ART, did not take their medication properly (UNAIDS, 2019). Moreover, Fox and Rosen (2010) found that

only 63% of the people who started ART remained in care after three years. These behaviours of sub-optimal adherence and non-retention can cause virologic rebound and selective drug-resistant viral variants, which are a public health concern as they can be transmitted to uninfected individuals (Cohen, 2009).

As ART becomes more universally available in South Africa, more research into long-term treatment success is necessary to prevent virologic rebound and the development of selective drug-resistant viral variants. This study aims to contribute to this by analysing potential factors of non-retention in HIV care, in the context of rural South Africa. To understand the role of the potential factors of non-retention, this study will first explore HIV treatment and therapy success more carefully after which it will introduce a socioecological approach which conceptualises all potential factors that can influence retention in HIV care. Next, through quantitative analysis potential predictors will be identified and discussed.

HIV treatment and therapy success

To achieve long-term treatment success by suppressing HIV, it is important to evaluate the different steps and identify crucial points in the treatment process (figure 1). Frequent testing is the first important step as it ensures that everyone that is HIV positive is diagnosed and can receive HIV treatment as soon as possible after contracting the virus (Smit, Hallett, Lange, Garnett, & de Wolf, 2008). Once diagnosed, people with HIV should be linked to care, where they can receive ART prescriptions and need to adhere to ART to suppress the HIV virus so that they can achieve treatment success (Mugavero, Amico, Horn, & Thompson, 2013).



As illustrated in figure 1, all of these steps influence the treatment success. However, only ART adherence and retention in care have a direct influence on treatment success (Mugavero et al., 2013). Low levels of ART adherence and retention in care are the most common cause for virological failure (Geng et al., 2010; Paterson et al., 2000). Virological failure, also understood as therapy failure, occurs when ART is unable to control the HIV infection and fails to sustain suppression of the viral load in the plasma. It is clinically defined as two consecutive viral load tests ≥ 1000 HIV RNA copies/ml (WHO, 2017).

As ART adherence has such a direct influence on virological failure, extensive research has been done since the introduction of the medicine in 1996 (Moore & Chaisson, 1999). Initial research on ART adherence was concerned with the levels required to suppress the virus. Paterson et al. (2000) found that the level of ART adherence required was at least 95%. However, more recent studies have suggested even lower levels of adherence between 85% and 89% (Viswanathan et al., 2015). Nevertheless, levels of adherence required for ART are relatively high and HIV positive people struggle to adhere to their medication (Ortego et al.,

2011). To understand these struggles various meta-analyses have been conducted and have identified sociodemographic (Ammassari et al., 2002), psychosocial (Ammassari et al., 2002; Gonzalez, Batchelder, Psaros, & Safren, 2011; Langebeek et al., 2014), condition related (Atkinson & Petrozzino, 2009), treatment-related (Atkinson & Petrozzino, 2009; Langebeek et al., 2014), interpersonal (Mills et al., 2006) and more structural factors (Ortego et al., 2011) which influence ART adherence behaviour.

Like ART adherence, retention in care influences treatment success directly. Only recently, the concept of retention in care has received more attention, as various studies have associated low retention in care with inconsistent ART receipt and adherence (Geng et al., 2010) as well as increased mortality, compared to patients in care (Mugavero et al., 2009; Tripathi, Youmans, Gibson, & Duffus, 2011). Retention in care can be understood as remaining connected to medical care once entered (Messerli, Abramson, Aidala, Lee, & Lee, 2002). More specifically for HIV positive people, Rosen, Fox, and Gill (2007) defined retention in care as the proportion of patients who are alive and on ART whilst being part of ART treatment programmes.

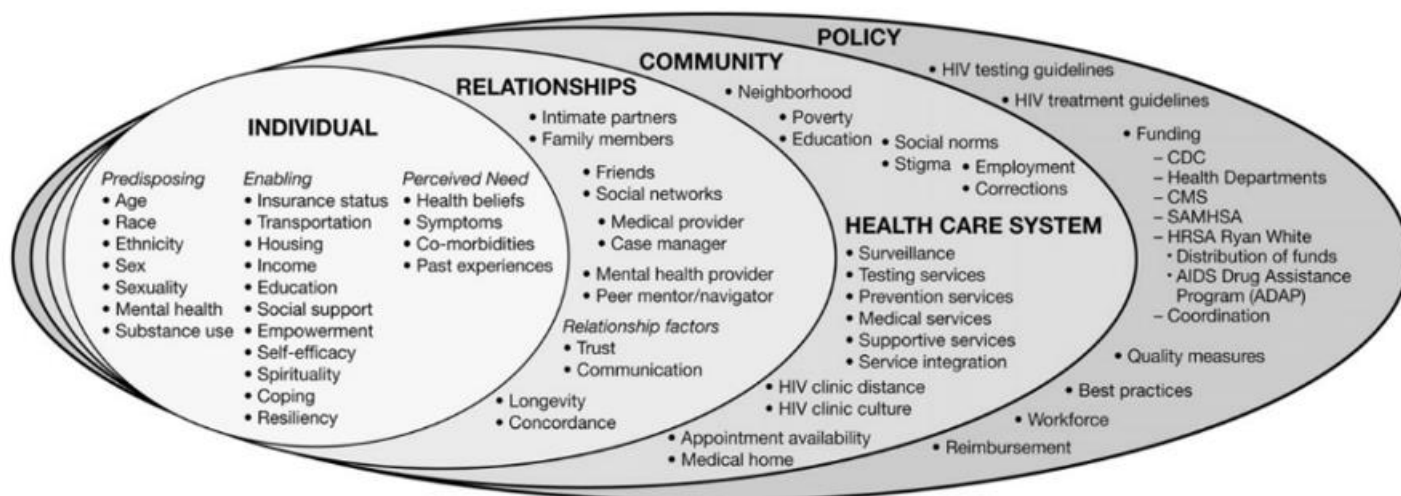
In a systematic review of retention in Sub-Saharan Africa, loss to follow-up (LTFU) was identified as the major cause of non-retention (Rosen et al., 2007). Though there is no set definition for LTFU, it can generally be understood as people whom become lost from treatment for a certain amount of time (Rosen et al., 2007). Various studies have researched this concept and found that LTFU is comprised of unrecorded deaths, alternative sources for ART or patients whom take an extended 'break' and only return when their condition worsens or until they find the necessary financials to continue (Rosen et al., 2007). Though the concept of LTFU is explored, knowledge on why people become LTFU is limited (Mberi et al., 2015).

Socioecological approach to loss to follow-up

To understand why people become LTFU this study will take a socioecological approach. This approach is not based on a single discipline or theory, rather it bridges several perspectives into one overarching paradigm (Stokols, 1996). The approach recognises that health behaviours such as retention in care, are influenced by a wide range of factors situated within and beyond the individual (Mugavero, Norton, & Saag, 2011). Through a multilevel approach, influences on different levels can be identified. In addition, the socioecological approach also shows that these multilevel influences are interactive and reinforcing (Stokols, 1996).

Mugavero et al. (2011) take a pragmatic approach and have created a socioecological framework that conceptualises the complex interactive and reinforcing factors that can play a role of engagement in HIV care in the United States (figure 2). They have identified factors on the individual, relationship, community, health care system and policy level. Within the individual level, the Anderson healthcare utilisation model plays an important role as it is comprised of predisposing factors, enabling factors and perceived need (Andersen, 1995). The Anderson healthcare utilisation model purposes that usage of healthcare services is dependent on these three factors. As can be observed in figure 2, examples of predisposing factors include factors such as age, race and sex. Enabling factors are related to attitudes, knowledge and insurance. Lastly perceived need depends on comorbidities and past experiences . The Anderson healthcare utilisation model has been criticised for not paying enough attention to culture and social interaction (Guendelman, 1991). However, in the conceptual framework of Mugavero et al. (2011) the individual level is surrounded by the other levels of the socioecological approach, overcoming this criticism. Figure 2 displays that factors in these outer layers are interdependent and can influence the individual level as well as each other.

Figure 2. Socioecological Framework of Retention in Human Immunodeficiency Virus Care



*Figure 2. This socioecological framework displays the potential factors that may influence retention in HIV care. Adapted from "Health care system and policy factors influencing engagement in HIV medical care: piecing together the fragments of a fractured health care delivery system," by M.J. Mugavero, W. E. Norton and M. S. Saag. 2011, *Clinical Infectious Disease*, p. 240.*

The socioecological framework proposed by Mugavero et al. (2011) is supported by previous investigations on factors associated with LTFU (Greig et al., 2012; Mberi et al., 2015; Rosen et al., 2007). Various studies have identified factors on the individual, such as being young, male and low literacy skills are risk factors for becoming LTFU (Alvarez-Uria, Naik, Pakam, & Midde, 2013; Fox & Rosen, 2010; Nakiwogga-Muwanga et al., 2014). Moreover, associations between LTFU and CD4-count, viral load and diseases stage have been identified (Alvarez-Uria et al., 2013; Mberi et al., 2015; Nakiwogga-Muwanga et al., 2014). On the relationship level, Mberi et al. (2015) found that having a committed partner was associated with LTFU. Other studies have identified factors on the community and health care system as integrated patient care, active outreach to patients and community based patient adherence have been found to support lower LTFU rates (Greig et al., 2012; Luque-Fernandez et al., 2013; Mberi et al., 2015). Although previous research has found associations between factors identified by Mugavero et al. (2011) and LTFU, the complete ecological framework has not

been tested. Therefore, in an attempt to be as inclusive as possible in understanding why people become LTFU, this study will use the socioecological framework of Mugavero et al. (2011).

This Study

This research is a sub-study of the ITREMA randomised clinical trial (RCT), an open-label RCT assessing intensified treatment monitoring strategy to prevent accumulation of drug resistance in Elandsdoorn, Limpopo, rural South Africa (Wensing, 2018). The main research question of this study is: “What is the extent of loss to follow-up and which factors, as identified in the socioecological framework of Mugavero et al. (2011), can be associated with loss to follow-up in the context of the ITREMA randomised clinical trial?”.

As this study is a sub-study of the ITREMA RCT, not all data, as purposed in the socioecological framework of Mugavero et al. (2011), are available. On the individual level data on age, sex, sexuality, mental health, substance abuse, housing, income, education, coping, health beliefs, symptoms, co-morbidities, past experiences and quality of life will be included. On the relationships level data on intimate partner(s), family members, friends, social network and medical provider are available. For the community level data on poverty, education, social norms, stigma and employment exist and for the health care system data on HIV clinic distance, clinic culture, supportive services and appointment availability are available. Unfortunately for the policy level no data were recorded and this level can therefore not be included in this study.

Most of the recorded factors are expected to be associated with LTFU in the bivariate analyses as Mugavero et al. (2011) argue that all factors in their model play a role in the engagement of care. Despite the wide range of influences not all of these factors are expected to be associated to LTFU in the multivariable analysis. Given that individuals can decide on their own behaviour by mediating influences through cognitive processes, this study expects

that factors on the individual level are most likely associated with LTFU in the multivariable analysis (Conner & Noman, 2015).

Methods

Study Design and Sample

The ITREMA RCT started in June 2015 and ended in March 2019. It was conducted at the Ndlovu Medical Centre, Elandsdoorn, Limpopo province, South Africa (Wensing, 2018). Approximately 3600 patients received treatment for HIV at this medical centre. Patients were eligible to participate in the ITREMA RCT when they were 18 years or older, HIV positive and were either ready to start ART treatment at Ndlovu Medical Centre or they had been on treatment for more than one year and had a most recent HIV-RNA viral load of below 1000 copies/mL, performed in the past six months. From June 2015 until August 2017 patients visiting the Ndlovu Medical Centre for a scheduled visit were recruited. The RCT consisted of nine study visits with a twelve week interval during a two year follow-up period. All participants provided written informed consent prior to entering the study. The study protocol was approved by the Research Ethics Committee of the Faculty of Sciences, University of Pretoria (Protocol 69/2015) and the Ethics Committee of the Limpopo provincial Department of Health.

Data Collection

At baseline participants completed two questionnaires consisting of 15 themes and 155 questions together with a research councillor . Additionally, a clinical assessment, in accordance with the South African National Department of Health HIV treatment guidelines, was performed by a trained nurse or physician at baseline. During the 12-week interval visits, data on pill count and self-reported adherence were collected as well as viral load.

Measures

Sociodemographic characteristics. Data on gender, age, education, residence, income, employment, household composition and relationship status were collected with questions from the National Income Dynamics Study wave 3 (Southern Africa Labour and Development Research Unit, 2016). To measure gender, participants were asked if they were women or men. For age, participants' date of birth was registered, which was converted to years of age for the analysis. Education was recorded according to the South Africa school system and categorised as primary (1-7, primary school), secondary (8-12, high school and college) and tertiary (13-14, university/vocational school). Participant's addresses were collected and the distance to clinic was calculated and dichotomised based on the median. Participants were asked about their employment status, which was dichotomised to employed/unemployed. Income and household income for salaries, businesses and financial support were recorded. Partnership status was recorded and dichotomised (yes/no) as well as number of household members. The number of household members were used to calculate the average income per household member, which was then dichotomised based on median. Data on food insecurity were measured by questions from The South Africa National Health Nutrition Survey (Shisana, Labadarios, et al., 2014). Food security was based on whether participants' households had run out of money to buy food during the past 12 months.

Risk behaviour. Questions regarding number of sexual partners in the last 12 months, duration of sexual relationship, condom usage and transactional sex were included through the UNAIDS sexual network questionnaire (Cleland, Konings, & Anarfi, 1998). Data on alcohol and drug abuse were collected through an in-house questionnaire that has been adapted to local circumstances (Ndlovu Care Group, 2014). As answers to questions on risk behaviour were limited, data were combined into the variable of risk behaviour. The variable is comprised of

transaction sex, alcohol usage and drug usage. If participant respond with yes on one of these questions they are identified with risk behaviour.

Depression. The Patient Health Questionnaire 9 (PHQ-9) was used to measure for symptoms of depression (Kroenke, Spitzer, & Williams, 2001). It used a 9-item scale in which symptoms of depression were assessed. Participants had to answer the following question for several symptoms: “Over the last 2 weeks, how often have you been bothered by any of the following problems?”. Answers were assessed on a 5-point scale. An example of a symptom was “feeling down, depressed, or hopeless”. The questionnaire had a Cronbach’s alpha of 0.85, indicating a good inter reliability. The total score was the sum of the answers and was divided into five categories. For this research, the score was dichotomised into depressive symptoms and no depressive symptoms.

Coping Styles. The use of different coping styles was assessed using the Coping Inventory for Stressful Situations (CISS) (Endler, Parker, de Ridder, & van Heck, 2004). Twenty-one questions followed the statement “During a difficult, stressful or upsetting situations, how often do you do the following...” The questionnaire distinguished three coping styles: *task*, *emotion* and *avoidance* coping. Each coping style was assessed with seven items where participants answered on a 5-point scale. An example item for task oriented coping was “Determine a course of action and follow it”. Emotion oriented coping included statements such as “Blame myself for having gotten into this situation” and avoidance-orientated coping included items like “Take some time off and get away from the situation”. Task oriented coping ($\alpha=0.93$), emotion oriented coping ($\alpha=0.81$) and avoidance orientated coping ($\alpha=0.79$) all had a good inter reliability. The total scores for each coping style, were calculated with the sum of the answers.

Health Literacy. The Brief estimate of Health Knowledge an Action HIV (BEHKA-HIV) version (Osborn, Davis, Bailey, & Wolf, 2010). Three open questions were asked to

assess participants' theoretical knowledge section An example of a question for the theoretical section was "What is a CD4-count?". The operational knowledge of participants was also assessed by five statements such as "I don't take ARV's when they make me feel bad" where patients could answer on a 3-point scale ranging from "agree" to "disagree". Patients could score three points for theoretical knowledge and five points for the operational knowledge, ranging the total score 0-8. Originally health literacy was organised into three levels, low (<4) middle (4-6) and high (7-8), however for the purpose of this study the score was dichotomised between low or middle and high literacy.

Physical health. Trained nurses and physicians collected clinical data, including disease history, medication use, ART history, WHO HIV staging and physical examination were recorded. Laboratory data including CD4+ T-lymphocyte counts and viral load were also measured as per RCT protocol. All data were abstracted into case report forms which were checked by a physician prior to capturing. This research used the variable on ART at baseline to represent whether or not a patient did have a HIV medical history prior to the study. Moreover, it incorporated WHO stage, in which comorbidities and general health are reflected. For this study it was dichotomised into two categories: no/minimal symptoms (stage I/II) versus severe symptoms (stages III/IV). Lastly, CD4 count was used, which was dichotomised into two categories of below 200 CD4 count and 200 or above. The division at 200 was made as this indicates an advanced HIV disease (WHO, 2017).

Adherence. As literature recommends to use at least two measurements for adherence, self-reported adherence and Pill count were used. (Osterberg & Blaschke, 2005). Self-reported adherence was measured using three questions from the ACTG questionnaire (Chesney et al., 2000). For self-reported adherence patients were considered to have a good adherence when all questions: "how often do you have difficulty in taking your medication on time? ", "on average how many days per week would you say that you missed at least on dose of your medication?"

and “when was the last time you missed taking any of your medications?”, were answered with never. Pill count was recorded in percentages and poor adherence was defined as pill count <95% and >105%. These values were chosen in accordance with the WHO (2017). Together these variables were combined into one variable where a participant was to considered to have good adherence when both variables were reported as having good adherence.

Quality of life. The quality of life was assessed using the WHO-QOL-HIV-BREF questionnaire (Pedroso, Gutierrez, Duarte, Pilatti, & Picinin, 2011). It consists of 29 items, which are divided into six domains. An example question that assesses the psychical domain is “How satisfied are you with your sleep?”. The psychological domain asks questions such as “How well are you able to concentrate? ”. One question for the level of independence asked “How well are you able to get around?”. For social relations an example includes “To what extent do you feel acceptable by the people you know?”. The assessment of environment is concerned with questions such as, “How safe do you feel in your daily life” whereas questions around the personal beliefs are concerned with questions like “To what extent do you feel your life to be meaningful?”. All answers were given on a 5-point scale. The quality of life score had a strong inter reliability of $\alpha=0.92$. The final score was calculated by adding the questions per domain together and using the following formula:

$$\text{Transformed scale} = \left[\frac{\text{actual raw score} - \text{lowest possible raw score}}{\text{possible raw score change}} \right] \times 100$$

Social support. Support from household and non-household members were both measured using the standardized questionnaire of the Netherlands Kinship Panel Study (de Hoon, Dykstra, Komter, Liefbroer, & Mulder, 2015). The questionnaire existed out of five items in which participant could indicate “to what extent household or non-household members supported you in....” One example included “In decisions about work or education”. Answers were recorded on a 4-point scale. Household support ($\alpha=0.92$) and non-household support

($\alpha=0.97$) both had a good inter reliability. The average of the five questions was used to calculate the total scores for both the household and non-household support.

Caregiver trust. An adapted version of ‘The Helping Alliance Questionnaire 2’ (HAQ-2) is used to assess therapeutic alliance (Luborsky et al., 1996). The original questionnaire includes nineteen questions that evaluate the relationship between a patient and his/her caregiver. Eleven of the questions focus on the trust in caregiver whilst the other seven focus on the caregiver as a psychotherapist. For this research, only the first eleven statements were included. An example of such a statement is “I feel that I can depend on the clinician”. Answers were on a 6-point scale. There was a strong inter reliability ($\alpha=0.84$) and the final score is the average of these eleven items, ranging from 1-6.

Stigma. To measure internalised HIV related stigma, the *AIDS-related stigma scale* of Kalichman and Simbayi (2003) was combined with the questionnaire developed by Herek, Capitano, and Widaman (2002). These questionnaires focused on internalised stigma of the participants. In the questionnaire participants were asked if they agreed with 13 statements. For example “People who have AIDS are dirty”. Answers were recorded on a 4-point scale. There was a strong inter reliability ($\alpha=0.91$) and the final score was the sum-score divided by thirteen.

Loss to follow-up. The outcome variable of LTFU was used as indication of retention in care. A participant was LTFU when he or she had not visited the clinic for more than 90 days after the last scheduled clinical visit date, and prior to end of study, without being transferred out or being documented as deceased. All other participants were categorised as in care.

Data Analysis

All data were analysed in R version 3.4.4. First frequencies, proportions, medians and interquartile ranges were calculated to describe the characteristics of the sample. Next, bivariate logistic regression analyses were performed to assess associations between individual potential

covariates and LTFU. Covariates that in the bivariate analyses were associated with LTFU ($P < 0.10$) were included in a multivariable logistic regression analysis. Factors were seen as significant covariates of LTFU when $P < 0.05$.

Results

Characteristics of the Study Sample

501 people were enrolled in the ITREMA RCT. Their baseline characteristics are given in table 1. The majority of the participants were women and middle aged. Few participants had a tertiary education and almost half of them were unemployed. Most participants did not engage in risky behaviour, such as transactional sex or substance abuse. Mental and physical health were relatively good as only a small number of participants were showing depressive symptoms and few participants were in WHO stage III or IV or had a CD4 count below 200. Roughly half of the participants had been on ART prior to the RCT. The majority of participants had good adherence and the overall quality of life for the sample is relatively high. The support system for the sample is mostly well-developed as household and non-household support and therapeutic alliance were reported as relatively high and stigma was reported as fairly low.

Table 1
Socio-demographic characteristics and adherence of ITREMA trial participants at baseline (N = 501)

	Frequency	Percentage	Median	Interquartile range
Gender				
Women	351	70.1		
Men	150	29.9		
Age			42.4	35.6-49.1
Level of Education				
Primary	93	18.6		
Secondary	377	75.3		
Tertiary	31	6.2		
Relationship				
Yes	225	45.0		
No	275	55.0		

Distance to Clinic				
≤ 30 kilometres	251	50.1		
> 30 kilometres	250	49.9		
Employed				
Yes	247	49.4		
No	253	50.6		
Household income per household member (ZAR)			666.70	296.90-22500.00
≤666.70	235	50.2		
>666.70	233	49.8		
Food insecurity				
Yes	32	6.4		
No	469	93.6		
Risk behaviour				
No	414	87.3		
Yes	60	12.7		
Depression				
No symptoms	468	93.6		
Symptoms	32	6.4		
Task orientated coping			18.0	12.0-25.3
Emotional orientated coping			14.0	11.0-19.0
Avoidance oriented coping			12.0	9.0-17.0
Health literacy				
Low or Middle	4	0.8		
High	491	99.2		
On ART at baseline				
No	207	41.3		
Yes	294	58.7		
Disease stage				
Stage I or II	450	90.9		
Stage III or IV	45	9.1		
CD4-count			376	(191-1400)
<200	114	26.1		
≥200	323	73.9		
Adherence				
Good	326	72.6		
Poor	123	27.4		
Quality of life			74.1	66.4-83.6
Household support			4.0	3.8-4.0
Non-household support			4.0	3.2-4.0
Therapeutic alliance			5.0	5.0-5.6
Stigma			1.8	1.2-2.0

Extent of loss to follow-up

After two years, 79 participants (15.8%) were categorised as LTFU. All other participants (n=422 [84.2%]) remained connected to the care of the Ndlovu Medical Clinic.

Bivariate and multivariable analyses

Detailed results of the bivariate and multivariable analyses are shown in table 2. Through bivariate logistic regression analyses, the following factors could be associated with LTFU ($P < 0.10$): gender, age, employment, food insecurity, risk behaviour, depression, task orientated coping, emotional orientated coping, avoidance orientated coping, on ART at baseline, disease stage, CD4-count, adherence, household support, non-household support, stigma and quality of life.

These variables were included in the multivariable analysis. Where age, depression, emotional orientated coping, avoidance orientated coping, adherence and quality of life were statistically significant with LTFU ($P < 0.05$). The model explains 56.4% of variance in becoming LTFU (Nagelkerke Pseudo R^2 : 0.564). Based on this model, participants were more likely to become LTFU when they were younger, had depressive symptoms, low developed emotional orientated coping styles, high developed avoidance orientated coping styles, poor adherence and a lower quality of life. Depression and adherence seemed to have a relatively large effect. Whereas age, emotional orientated coping abilities, avoidance orientated coping abilities and quality of life had smaller effects.

Table 2
Bivariate and multivariable analyses of loss to follow-up (N=501)

	Bivariate Analyses		Multivariable Analysis	
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Gender				
Women	<i>Ref.</i>		<i>Ref.</i>	
Men	1.75 (1.06-2.87)	0.027	2.17 (0.70-6.84)	0.178
Age	0.091 (0.89-0.94)	<0.001	0.91 (0.86-0.96)	<0.001
Level of Education				
Low	<i>Ref.</i>			
Middle	1.91 (0.96-4.25)	0.086		
High	2.24 (0.69-6.84)	0.160		
Relationship				
Yes	<i>Ref.</i>			
No	0.92 (0.57-1.49)	0.721		
Distance to Clinic				
≤ 30 kilometres	<i>Ref.</i>			
> 30 kilometres	0.86 (0.53-1.40)	0.553		
Employed				
Yes	<i>Ref.</i>		<i>Ref.</i>	
No	2.25 (1.37-3.79)	0.002	1.70 (0.59-5.05)	0.327
Household income per household member (ZAR)				
≤666.70	<i>Ref.</i>			
>666.70	0.67 (0.40-1.12)	0.131		
Food insecurity				
Yes	<i>Ref.</i>		<i>Ref.</i>	
No	0.45 (0.21-1.06)	0.053	2.56 (0.44-18.91)	0.321

Risk behaviour				
No	<i>Ref.</i>		<i>Ref.</i>	
Yes	5.45 (2.99-9.87)	<0.001	2.60 (0.78-8.91)	0.120
Depression				
No symptoms	<i>Ref.</i>		<i>Ref.</i>	
Symptoms	11.78 (5.55-26.04)	<0.001	11.32 (2.44-61.58)	0.003
Task orientated coping	1.10 (1.07-1.14)	<0.001	1.08 (0.996-1.17)	0.064
Emotional orientated coping	1.10 (1.05-1.15)	<0.001	0.84 (0.73-0.95)	0.007
Avoidance oriented coping	1.09 (1.05-1.14)	<0.001	1.14 (1.03-1.27)	0.013
Health literacy				
Low or Middle	<i>Ref.</i>			
High	0.53 (0.07-10.84)	0.587		
On ART at baseline				
No	<i>Ref.</i>		<i>Ref.</i>	
Yes	0.06 (0.02-0.12)	<0.001	0.027 (0.05-1.10)	0.084
WHO stage				
Stage I or II	<i>Ref.</i>		<i>Ref.</i>	
Stage III or IV	4.25 (2.18-8.14)	<0.001	0.75 (0.13-3.87)	0.739
CD4-count				
<200	<i>Ref.</i>		<i>Ref.</i>	
≥200	0.41 (0.24-0.70)	<0.001	2.01 (0.64-6.74)	0.239
Adherence				
Good	<i>Ref.</i>		<i>Ref.</i>	
Poor	4.12 (2.19-7.89)	<0.001	6.82 (2.31-22.64)	<0.001
Quality of life	0.92 (0.90-0.95)	<0.001	0.90 (0.85-0.96)	<0.001
Household support	0.56 (0.41-0.77)	<0.001	0.79 (0.41-1.58)	0.487
Non-household support	0.59 (0.48-0.74)	<0.001	1.09 (0.68-1.76)	0.726
Therapeutic alliance	1.47 (0.87-2.46)	0.144		
Stigma	0.45 (0.25-0.81)	0.008	0.55 (0.15-1.92)	0.353

Discussion

This study assessed the extent of the retention rate after a period of two years and found a retention rate of 84.2%. This is relatively higher than the overall retention rate after two years of 70%-77% found in the meta-analysis of Fox and Rosen (2010). The higher retention rate of this study could be explained by the context of this study. This research is a sub-study of the ITREMA RCT, which examines an intensified adherence support and monitoring intervention at the Ndlovu Medical Centre. The intensified monitoring and support at a high quality health care facility, could explain the high retention rates of this study.

Despite the relative high retention rate, 15.8% of the participants still became LTFU. Following the socioecological model of Mugavero et al. (2011) this study assessed a wide range of variables in an attempt to identify which factors could be associated with LTFU. In line with the expectations of the socioecological model, most variables seemed to have an effect on LTFU in the bivariate analyses. Therefore seventeen out of the twenty-three factors were included in the multivariable analysis. Here, age, depression, emotional orientated coping styles, avoidance orientated coping styles, adherence and quality of life were found to be associated with LTFU. As expected, all of these factors were part of the individual level of the socioecological model.

On the individual level, this study found, similarly to other studies (Alvarez-Uria et al., 2013; Wandeler et al., 2012), that younger participants were more likely to become LTFU. A possible reason for this could be that younger people may not have developed the skills necessary to manage a chronic disease as they struggle to navigate themselves through complex healthcare systems (Kranzer et al., 2017). However, no associations with other sociodemographic variables have been found whilst other studies reported associations between LTFU and being male and low literacy skills (Alvarez-Uria et al., 2013).

Additionally, depressive symptoms were strongly associated with higher chances of becoming LTFU. This is in line with previous studies whom have identified mental health as a significant barrier to HIV-care (Gonzalez et al., 2011). In the meta-analysis of Rooks-Peck et al. (2018), it was found that mental health problems of HIV positive people are related to poor retention in health. Following mental health, emotional and avoidance coping styles were also found to influence LTFU. Previous research had similar findings as coping styles are known to influence mental health, which in turn affects LTFU (Miller & Major, 2000; Steward et al., 2008). In accordance with previous studies (Moneyham et al., 2010), this research identified better developed emotional coping styles with a lower chance to become LTFU. Contrastingly, it found that better developed avoidance coping styles increased the chance of becoming LTFU.

Furthermore, it was found that adherence had a relatively great influence on the individual level as participants were almost seven times more likely to become LTFU with poor adherence. Though comparable research was limited, it can be said that other studies have found similar results. Poor adherence can result in virologic failure, which was found to be associated with LTFU (Mberi et al., 2015; Nakiwogga-Muwanga et al., 2014). Moreover, other studies have also highlighted that depression is associated with poorer adherence (Gonzalez et al., 2011). Despite the association of poor adherence, this study did not associate disease stage and CD4 count with LTFU whilst other findings did (Alvarez-Uria et al., 2013; Nakiwogga-Muwanga et al., 2014). One explanation for this could be that in more resource constrained settings of other studies, treatment is dependent on WHO stage or CD4-count which may then account for these findings (Mberi et al., 2015).

Lastly, quality of life was found to be associated with LTFU on the individual level. No association between quality of life and LTFU were found in other studies as no analyses have been found. However, other studies have reported that quality of life is closely associated with

depressive symptoms as well as adherence, which have both been strongly associated with LTFU in this study (Ammassari et al., 2002; Ezeamama et al., 2016; Mills et al., 2006).

This study has not associated factors on the relationship, community or healthcare system level in the multivariable analysis. Limited social support and non-integrated care were identified as risk factors by other studies (Alvarez-Uria et al., 2013; Greig et al., 2012; Wandeler et al., 2012), but were not found significant in this study. This could be explained by the context of this study as roughly half of these participants received intensified care and support, relationships might have less of an effect in this study. Moreover, unlike several studies no association was found between stigma and LTFU (Katz et al., 2013; Persons, Kershaw, Sikkema, & Hansen, 2010). The lack of association might be explained by the overall low stigma score of this study.

Strengths and Limitations

One of the major strengths of this study is the extensive number of variables available, which were carefully collected over the course of two years. Nevertheless, some limitations should be taken into account when interpreting these results. Firstly, there is no clear definition of LTFU. Though this paper has a carefully considered definition, when comparing results of this study with other studies one should be mindful of the differences between definitions.

Secondly, despite the extensive collection of variables and the attempts of this study to be as inclusive as possible, important factors might have not been taken into account as it was impossible to include all factors purposed by Mugavero et al. (2011). Influences on a higher socioecological level were especially difficult to include as all data were collected through the participants. Therefore, it is recommended that a more qualitative approach is taken to see if and how factors from higher socioecological levels influence the individual participants.

Another limitation of this study is the potential social desirability bias as participants were assisted by councillors to complete questionnaires. HIV is a complex and delicate issue in South Africa, which might make it difficult for participants to talk about it. The distribution of some potential covariates such as stigma and therapeutic alliance suggest that there was a social desirability bias as the distribution of stigma was low and the distribution of therapeutic alliance high. Moreover, results of avoidance coping showed inconsistency with previous studies, which might be explained by social desirability bias. Additionally, participants received their treatment at the same clinic as where the research took place. This might also have influenced answers of patients as they might have believed that their treatment could depend on their answer. In an attempt to overcome these limitation and provide a more representative sample, some variables were combined (e.g. risk behaviour), however this could not be done for all variables. Therefore, for future research, it would either be recommended that councillors are better trained so they can better explain the importance of honest answering to participants or an audio computer-assisted self-interview software could be used, allowing participants to answer questions in private.

Lastly, it needs to be considered that most of the data used in this study were collected at baseline. Whilst, most of these data do not change over time, some such as mental health, social support and therapeutic alliance might have changed overtime. Therefore in future research, it might be beneficial to collect these data during follow-up visits as well.

Conclusion

In conclusion, this study has contributed to research into long-term treatment success by analysing a wide-range of potential factors of non-retention in HIV care, in the context of rural South Africa. It identified that age, depressive symptoms, emotional and avoidance coping styles and quality of life influence the chance of participants to become LTFU. These findings

highlight that in addition to universal treatment, the South African government should provide additional support and monitor the overall well-being of HIV infected individuals to achieve long-term treatment success. More specifically, healthcare providers should screen for depressive symptoms and poor adherence among HIV positive people as this increases the risk to become LTFU. Additionally, extra support should be provided in developing coping styles. The extra support and monitoring should especially address the younger HIV infected people.

However, these recommendations and results should be viewed with care as more research into why people become LTFU is required. Various studies have been conducted on this topic, but there has not been a synthesis of evidence. Therefore this research would recommend that a systematic review will be done of all available factors associated with LTFU.

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