The social and clinical characteristics of patients on antiretroviral therapy who are 'lost to follow-up' in KwaZulu-Natal, South Africa: a prospective study

Karl Peltzer, Shandir Ramlagan, Mohamed Salim Khan, Bernhard Gaede

Abstract

A significant proportion of those initiating antiretroviral treatment (ART) for HIV infection are lost to follow-up. Causes (including HIV symptoms, quality of life, depression, herbal treatment and alcohol use) for discontinuing ART follow-up in predominantly rural resource-limited settings are not well understood. This is a prospective study of the treatment-naïve patients recruited from three (one urban, one-semi-urban and one rural) public hospitals in Uthukela health district in KwaZulu-Natal from October 2007 to February 2008. The aim of this study was to investigate predictors of loss to follow-up or all caused attrition from an ART programme within a cohort followed up for over 12 months. A total of 735 patients (217 men and 518 women) prior to initiating ART completed a baseline questionnaire and 6- and 12-months' follow-up. At 12-months follow-up 557 (75.9%) individuals continued active ART, 177 (24.1%) were all cause attrition, there were 82 deaths (13.8%), 58 (7.9%) transfers, 7 (1.0%) refused participation, 8 (1.1%) were not yet on ART and 22 (3.0%) could not be traced. Death by 12-months of follow-up was associated with lower CD4 cell counts (risk ratio, RR=2.05, confidence intervals, CI=1.20 - 3.49) and higher depression levels (RR=1.05, CI=1.01 - 1.09) at baseline assessment. The high early mortality rates indicate that patients are enrolling into ART programmes with far too advanced immunodeficiency; median CD4 cell counts 119 (IQR=59 - 163). Causes of late access to the ART programme, such as delays in health care access (delayed health care seeking), health system delays, or inappropriate treatment criteria, need to be addressed. Differences in health status (lower CD4 cell counts and higher depression scores) should be taken into account when initiating patients on ART. Treating depression at ART initiation is recommended to improve treatment outcome.

Keywords: *Antiretroviral treatment, loss to follow-up, KwaZulu-Natal, South Africa.*

Résumé

Une importante proportion des personnes débutant un traitement aux antirétroviraux (ART) afin de lutter contre une infection par le VIH est perdue de vue. Les causes (et notamment les symptômes du VIH, la qualité de vie, la dépression, les traitements à base de plantes et la consommation d'alcool) de l'interruption du traitement aux ART, pour l'essentiel dans des environnements ruraux caractérisés par des ressources limitées, ne sont pas bien comprises. Ce document est une étude prospective du traitement de patients naïfs recrutés dans trois hôpitaux publics (l'un étant situé en zone urbaine, un autre en zone semi-urbaine et le dernier en zone rurale) dans le district sanitaire d'Uthukela, dans le KwaZulu-Natal d'octobre 2007 à février 2008. L'objectif de cette étude était d'étudier les indicateurs prévisionnels des perdus de route ou de tout retrait provoqué d'un programme de traitement aux ART dans une cohorte suivie pendant plus de 12 mois. Au total, 735 patients (217 hommes et 518 femmes) ont répondu à un questionnaire de référence avant de débuter leur traitement, puis à un questionnaire de suivi à 6 et à 12 mois. Lors du suivi à 12 mois, 557 (75,9 %) des participants poursuivaient le traitement aux ART, 177 (24.1%), 82 étaient décédés (13.8%), 58 (7.9%) avaient été transférés, 7 (1.0%) ont refusé de participer, huit (1.1%) n'étaient toujours pas sous ART et 22 (3.0%) n'ont pu être retrouvés. Les décès dans les 12 mois du suivi étaient associés à un compte de CD4 réduit (rapport

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de risque, RR=2.05, intervalle de confiance, IC=1.20 – 3.49) et des niveaux de dépression plus élevés (R =1.05, IC=1.01 - 1.09) lors de l'évaluation de référence. Les forts taux de mortalité précoce indiquent que les patients s'inscrivent aux programmes d'ART alors que leur immunodéficience est déjà beaucoup trop avancée et avec un compte de CD4 médian de 119 (intervalle interquartile = 59 - 163). Les causes de l'accès tardif au programme d'ART, telles que les retards dans l'accès aux soins de santé (recherche de soins de santé retardée), les retards du système de santé ou les critères de traitement inappropriés, doivent être traitées. Les différences dans l'état de santé (compte de CD4 et taux de dépression supérieurs) doivent être prises en compte lorsque les patients débutent les ART. Le traitement de la dépression à l'initiation du traitement aux ART est recommandé afin d'améliorer les résultats du traitement.

Mots clés: *Traitement antirétroviral, perdus de vue, KwaZulu-Natal, Afrique du Sud.*

Introduction

Many HIV-infected individuals in African countries including South Africa present for HIV/AIDS care and treatment late in disease progression, with very low CD4 counts (Fairall *et al.*, 2008; Rosen, Long, & Sanne, 2008; Larson *et al.*, 2010). In ART programmes in resource-limited settings a substantial minority of adults lost to follow-up cannot be traced, and among those traced 20 - 60% had died (Brinkhof, Pujades-Rodriguez & Egger, 2009; Brinkhof *et al.*, 2010; Boulle *et al.*, 2010). Fox and Rosen (2010) estimated the proportion of all-cause adult patient attrition from antiretroviral therapy (ART) programmes in service delivery settings in sub-Saharan Africa through 36 months on treatment and found that loss to follow-up was the most common cause of attrition (59%), followed by death (41%). Median attrition at 12 months was 22.6% (range 7 - 45%) (Fox & Rosen, 2010).

Factors associated with all-cause loss to follow-up from the ART programme include transfer out (Brinkhof *et al.*, 2009), financial reasons (Brinkhof *et al.*, 2008, 2009), improving or deteriorating health such as lower baseline CD4 cell count, higher initial HIV RNA load, and loss of weight on ART (Brinkhof *et al.*, 2009; Coetzee *et al.*, 2004; Dalal *et al.*, 2008; Fox, Brennan, Maskew M, MacPhail & Sanne, 2010), stigma and social problems (Brinkhof *et al.*, 2009), adverse effects of antiretroviral drugs, socio-demographic factors such as age at ART initiation (Dalal *et al.*, 2008), men (Cornell, Myer, Kaplan, Bekker & Wood, 2009), being employed (Larson *et al.*, 2010) alcohol and drug abuse (Deribe *et al.*, 2008), depression (Hartzell, Janke & Weintrob, 2008) and the use of local herbal remedies (Reid, Mulenga, Folk, Tambatamba, & Chi, 2008).

The aim of this study was to assess social and clinical factors (including HIV symptoms, quality of life, depression, herbal treatment and alcohol use) of loss to follow-up from an ART programme in a predominantly rural resource-limited setting within a cohort study over 12 months.

Method

Cohort

The Uthukela Health District has a population of 553 671 and comprises five local authority areas. The district has one regional and two district hospitals, one private hospital, three primary health care facilities, 24 fixed clinics and 17 mobile clinics with 177 visiting points (KwaZulu-Natal Department of Health, 2007). Initiation on ART is done at the three public hospitals. Some patients are referred to primary care clinics for ARV collection but return to the hospital for 6-monthly medical visits. In one, the rural, site, the ARV service had been decentralised and patients who had been referred to the primary care clinic would be followed up at the primary care clinic, rather than the hospital site.

Design

Prospective observational cohort study of treatment naïve patients recruited from three public hospitals (one urban, one semi urban and one rural) in Uthukela health district in KwaZulu-Natal from October 2007 to February 2008. ART-naïve patients, >18 years of age, who were about to commence ART (at ART initiation) at one of the three HIV clinics during the recruitment period were eligible for this study. Adults were considered eligible for ART with a prior AIDS diagnosis (WHO stage IV disease) or a CD4 count <200 cells/mm^3. Patients are required to attend a series of counselling visits during the pre-treatment phase stressing the importance of adherence to ART medications. The first-line therapy for treatment-naïve patients consisted of two nucleoside reverse transcriptase inhibitors (NRTIs), stavudine (d4T) and lamivudine (3TC), along with a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV) or nevirapine (NVP). Patients attend the ART clinic each month, at which time they are given another month's supply of ART drugs.

Sampling procedure and recruitment

Systematic sampling was used by asking health care providers for referrals of ART-naïve patients eligible for ART (CD4 count <200 cells/mm^3) who had yet to commenced treatment. Health care providers from the three selected public HIV clinics asked every sequentially visiting patient meeting the inclusion criteria if they would like to complete a confidential survey and interview regarding their health and social situation. Each clinic enrolled at least 200 patients, for a total of 600.

The interview included information gathered from a medical record review on details of medical conditions, laboratory tests and treatment, social and health status and utilisation of herbal treatments for HIV. It was made clear to patients that their participation in this study was voluntary and a decision not to participate would not affect their medical care. If the potential participant indicated an interest in participating, the health care provider then referred them to an external Human Sciences Research Council (HSRC) research assistant. Before the survey was administered, individuals were given background information

on the study then, if they agreed to participate, asked to sign and complete a consent form before the interview took place in a private area in or outside the clinic.

The interviews were conducted by four external HSRC researchers (one or two per HIV clinic) trained in interview administration of a questionnaire. Permission to access patient medical records was sought from both the patient and the health worker/manager at each clinic. Questionnaires were anonymised, with no personal identifying information recorded on them. Recruitment took place over a period of four months, with 97.8% participation rate. The questionnaire was translated into the major language spoken in the study area (Zulu) and back translated by a second translator. Inconsistencies found during verification were corrected. Pre-testing of the questionnaire was completed with five HIV-positive persons not involved in the study.

Patients discontinuing follow-up, defined here as missing (over a month) the 6- and/or 12-month scheduled study follow-up appointment as part of the cohort study and having missed the clinic appointment for two consecutive months, were traced by the interviewers. Tracing was conducted by telephone contact (up to five times) with patients or their families using contact information collected at baseline. Home visits (up to three times) were attempted if telephone contact was unsuccessful. On contact with the patient of family member, health status (e.g. living, deceased) and reasons for loss to follow-up were determined. In trying to establish the true cause of loss to follow-up, the Department of Home Affairs (DHA), were contacted to verify if untraceable patients were deceased according to their death registry. In order to achieve this, the HSRC unique patient identity number was cross referenced with the district hospital file numbers to establish the South African national identity numbers of untraceable patients. These national identity numbers were then submitted to the South African DHA, for verification of vital status.

Ethics approval was obtained from the HSRC ethics committee (Protocol number: REC 5/15/08/07) and approval was obtained from the Provincial Department of Health in KwaZulu-Natal.

Measures

Patients were interviewed with an anonymous questionnaire that requests information on socio-demographic characteristics, clinical history and health-related characteristics and health beliefs. Clinical data relating to date of HIV diagnosis, HIV acquisition and transmission risk factors, current CD4 cell count and viral load (Chiron 3.0 bDNA) was obtained from patients' medical charts.

The Revised Signs and Symptoms Checklist for Persons with HIV Disease

The SSC-HIVrev is a 72-item checklist of HIV/AIDS specific physical and psychological symptoms, scored using the following scale: 0 = not present today, 1 = mild, 2 = moderate and 3 = severe (Holzemer, Hudson, Kirksey, Hamilton & Bakken, 2001). Female-specific symptoms were removed, reducing the total to 64 (Peltzer, Friend-du Preez, Ramlagan & Fomundam, 2008). An HIV symptom index (symptom intensity) was created which weights each symptom's presence (0 or 1) by a rating of 1 - 3 (mild, moderate or severe), resulting in a range of 0 - 64 symptoms. Validity and reliability of the instrument have previously been reported for a US sample (Holzemer *et al.*, 2001) and various African countries (Makoae *et al.*, 2005) including South Africa (Peltzer & Phaswana-Mafuya, 2008b); reliability estimates from 0.76 to 0.94. The Cronbach alpha reliability coefficient of this 64-item scale was 0.95 at baseline in this study.

We assessed *depressive symptoms* using the 10-item version of the Centers for Epidemiologic Studies Depression Scale (CES-D) (Andresen, Malmgren, Carter, & Patrick, 1994). The CES-D has been widely used in studies of the relationship between HIV and depression (e.g. Kilbourne *et al.*, 2002) including in Southern Africa (Pearson *et al.*, 2009; Wingood *et al.* 2008); with reliability estimates of 0.76 (Pearson *et al.*, 2009). While the CES-D 10-item survey has not been directly compared to clinical diagnosis of major depression, the sensitivity and specificity of the CES-D 20-item survey has been reported to average 80% and 70%, respectively, compared to formal diagnostic interview (Mulrow, Williams, Gerety, Ramirez, Montiel, & Kerber, 1995). Cronbach's alpha for this sample was 0.82.

Alcohol Use Disorder Identification Test (AUDIT)-C was used to assess the consumption of alcohol in patients (i.e. frequency of drinking, the quantity consumed at a typical occasion and the frequency of heavy episodic drinking) (Babor, Higgens-Biddle, Saunders & Monteiro, 2001). Heavy episodic drinking is defined as the consumption of six standard drinks or more on a single occasion. In South Africa a standard drink is 12 g alcohol. The AUDIT-C has been validated in South Africa (Peltzer, Simbayi, Kalichman, Jooste, Cloete, & Mbelle, 2007). Because AUDIT is reported to be less sensitive at identifying risk drinking in women (Freeborn *et al.*, 2000), the cut-off points of binge drinking for women were reduced by one unit as compared with men, as recommended by Freeborn *et al.* (2000). Gordon *et al.* (2001) recommended a cut-off point of three and an even lower cut-off point for persons on ART; thus a cut-off of two was used in this sample of (pre) ART patients. The quantity and frequency of alcohol consumption that constitute a measurable harm for HIV patients has yet to be established and are likely to be lower than amounts recommended for general populations (Conigliaro, Justice, Gordon, Bryant, VACS Alcohol and Behavior Change Research Group, 2006). Cronbach alpha for the AUDIT-C in this sample was .87, indicating excellent reliability.

Herbal treatment for HIV

Herbal treatment was assessed with one item, 'Have you ever used herbal therapies (such as Ginseng, Echinacea or St. John's Wort, Hypoxis plant or African potato) for HIV in the past six months?'

Quality-of-life (QoL) domains embedded in the World Health Organization Quality of Life (WHOQOL)-HIV scales include questions regarding physical, psychological, social and environmental. Of the 31 items, 26 are identical to those of the generic WHOQOL-HIV BREF, thus enabling comparison of scores with those of healthy populations. The WHOQOL-HIV BREF produces six domain scores, which denote an individual's subjective perception of their own QoL in the following domains:

physical, psychological, level of independence, social relationships, environment, and spirituality. The individual items are rated on a 5-point Likert scale, where one indicates 'low, negative perceptions' and five indicate 'high, positive perceptions'. Domain scores are scaled in a positive direction, where higher scores denote higher perceived QoL. Items are organised by type of response-scale (capacity, frequency, intensity or satisfaction). The mean score of items within each domain is used to calculate the domain score; mean scores are then multiplied by four, so that the domain scores range between four and 20 (World Health Organization, 2002). In a previous study in South Africa with the same scale a Cronbach α reliability coefficient of 0.72 was found (Peltzer & Phaswana-

Table 1. Sample characteristics of patients at baseline assessment and study attrition analysis

	Baseline (*N*=735)		**12-months follow-up (*N*=557)**		**χ^2 or *t* test**	***p***
Variable	N or M	% or SD	N or M	% or SD		
Sex						
Male	217	29.5	158	72.8	1.48	0.224
Female	518	70.5	399	77.0		
Age, range 18 - 67	35.9	9.7	36.1	9.4	.98	0.326
Age in years						
18 - 28	171	23.3	121	21.7	3.06	0.080
29 - 39	336	45.7	264	47.4	2.62	0.105
40 - 50	159	21.6	121	21.7	.01	0.916
51 - 67	69	9.4	51	9.2	.15	0.703
Education						
Grade 7 or less	279	37.8	212	38.2	.01	0.934
Grade 8 - 11	314	42.8	245	44.1	1.46	0.227
Grade 12 or more	139	18.9	98	17.7	2.65	0.104
Missing	3	0.4	2	0.4		
Marital status						
Never married	522	71.0	399	72.3	.26	0.609
Currently married/cohabitating	163	22.2	121	21.9	.33	0.565
Separated/Divorced	15	2.0	12	2.2	.14	0.709
Widowed	27	3.7	20	3.6	.05	0.818
Missing	8	1.1	5	0.9		
Residence						
Rural (village)	338	46.0	246	44.4	3.10	0.079
Rural (farm)	125	17.0	99	17.9	.96	0.328
Urban (informal settlements)	41	5.6	35	6.3	2.17	0.141
Urban (formal settlements)	227	30.9	174	3.4	.13	0.714
Missing	4	0.5	3	0.5		
Household income						
Formal salary	215	29.3	174	31.8	3.92	0.048
Family member contributions	133	18.1	95	17.3	1.97	0.197
Social grants	264	35.9	205	37.4	.54	0.461
No income	57	7.8	39	7.1	2.01	0.156
Other	51	6.9	35	6.3		
Missing	15	2.0	9	1.6		
Time since HIV diagnosis						
≤1 year (2007/8)	540	73.5	409	73.4	.00	0.965
1-2 years (2006)	73	9.9	58	10.4	.60	0.441
>2 years (2005-1995)	122	16.6	90	16.2	.32	0.570
CD4 count (cells/μl) (median=119; IQR=59-163)						
<100	339	46.2	247	46.0	3.41	0.065
≥100	367	50.0	290	54.0		
Missing	28	3.8	20			
Herbal treatment for HIV	269	36.7	213	38.2	2.52	0.112
HIV symptoms index (range 0 - 64)	7.5	9.8	7.2	9.5	-1.38	0.167
Depression score (range 10 - 40)	16.1	7.8	15.9	7.8	-1.47	0.142
Hazardous or harmful alcohol use (AUDIT score ≥2)	53	7.2	39	7.0	.15	0.698
Health-related quality of life (range 6 - 30)	13.5	7.8	13.5	2.1	1.44	0.149

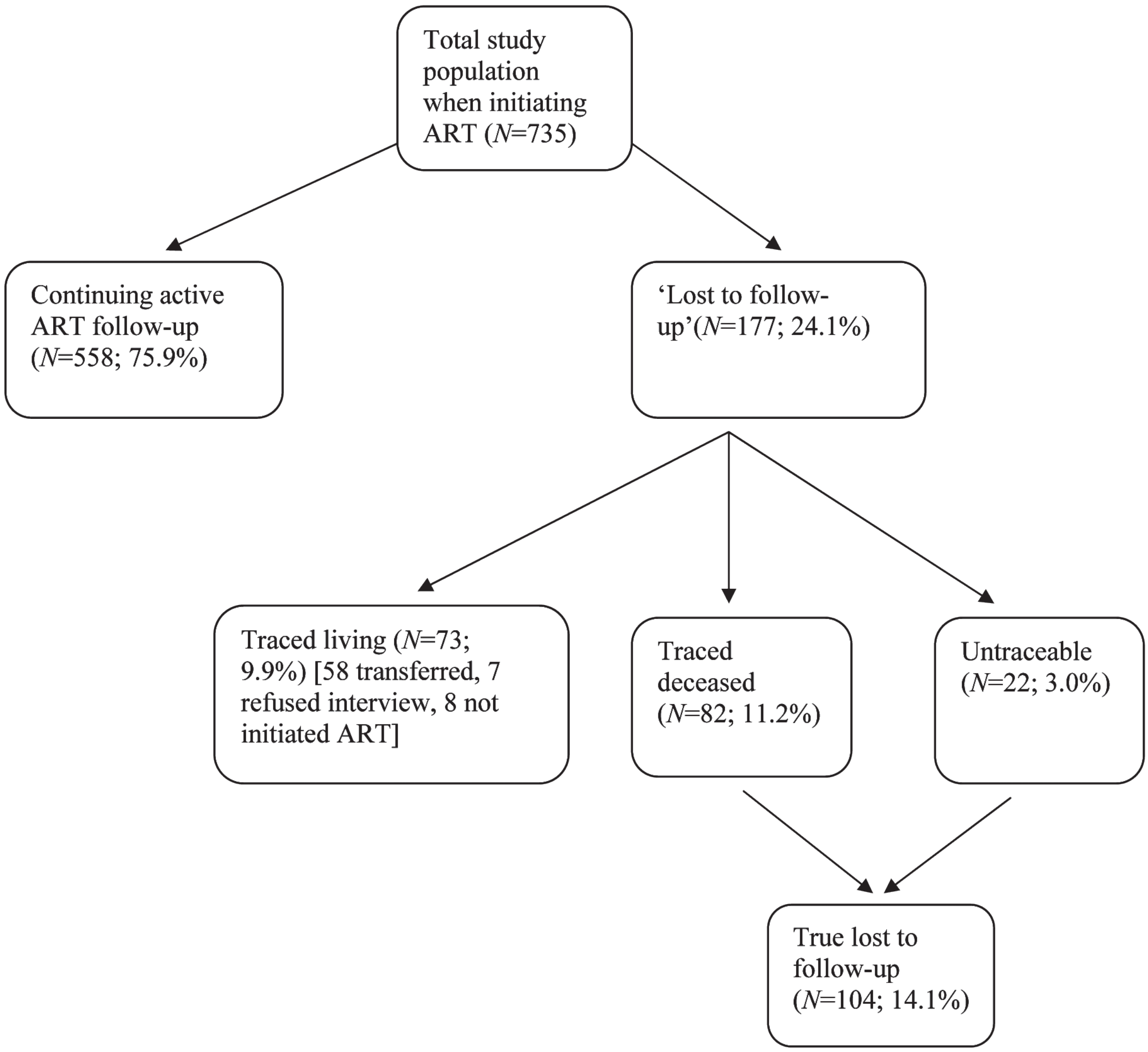

Fig. 1. Flow diagram of patient outcomes included in the study.

Mafuya, 2008a). The Cronbach α reliability coefficient of this 29-item scale was 0.80 at baseline in this sample.

Data anaysis

Data analysis was performed using STATA software version 10.0 (Stata Corporation, College Station, TX, USA). Descriptive statistics (proportions, means, median, inter quartile range, and standard deviations) were used to characterise the study sample at baseline. Chi-square tests and student independent T tests were used for the attrition analyses. The outcomes of interest were 'loss to follow-up', traced living, dead, untraceable. Log-binomial regression was used to estimate relative risks. The relative risk model included the following patient-specific factors at baseline as potential confounders (age, sex, marital status, education, geolocality, household income, CD4 cell counts, herbal treatment, HIV symptoms, alcohol use, depression and quality of life scores).

Results

Sample characteristics

The majority of participants (70.5%) were women; the mean age was 35.9 years (SD=9.7) and the educational level of the majority (80.7%) was less than Grade 12. Almost three-quarters (71.0%) were never married and for 264 (35.9%) social grants were the main source of the household income, followed by having a formal salary (29.3%) and family member contributions (18.1%). Almost two-thirds of the participants (63.0%) resided in a rural area. Most participants (73.5%) had been recently (within the past year) diagnosed as being HIV-positive. On average participants reported 7.5 HIV-related symptoms at the day of the interview. Depression scores were 16.1 and Health-related Quality of Life scores 13.5 at the baseline assessment. Fifty-three patients (7.2%) reported hazardous or harmful alcohol use and 36.7% were taking herbal treatment for HIV or HIV-related symptoms. Half of the sample (50%) had a CD4 cell count below 100. Study attrition analysis comparing participants who left the study with those who stayed found significant differences in terms of formal salary as household income (which is probably a function of increased mobility in getting work in urban areas) who stayed in the study and no significant differences in terms of gender, age, education, residence, time since HIV diagnosis, CD4 cell counts, HIV symptoms, depression and Health related quality of life scores, hazardous or harmful alcohol use and herbal treatment for HIV (see Table 1).

Table 2: Relative risks of loss to follow-up, traced living, traced diceased and untraceable based on log-binomial regression adjusted for age, sex, marital status, education, geolocality, household income, CD4 cell counts, herbal treatment, HIV symptoms, depression, alcohol use and quality of life score

	Loss to follow-up (A) *N*=177		**Traced living[1] (B)** *N*=73		**Traced deceased (C)** *N*=82		**Untraceable (D)** *N*=22	
	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Male v. female	1.21 (0.88-1.67)	0.247	0.97 (0.51-1.84)	0.929	1.21 (0.70-2.08)	0.496	1.91 (0.87-4.18)	0.105
Age (at initiation of ART)	0.99 (0.97-1.01)	0.209	0.94 (0.91-0.98)	0.001	1.03 (1.00-1.06)	0.090	0.97 (0.93-1.02)	0.232
Never married/divorced/separated/widowed v. Married/cohabitating	0.70 (0.51-0.97)	0.034	0.51 (0.28-0.93)	0.029	0.90 (0.48-1.71)	0.758	0.77 (0.33-1.81)	0.553
Formal education								
Grade 7 or less	1.00		1.00		1.00		1.00	
Grade 8-11	0.93 (0.65-1.33)	0.689	0.93 (0.49-1.78)	0.833	1.03 (0.53-2.00)	0.934	0.81 (0.33-1.95)	0.635
Grade 12 or more	1.22 (0.80-1.86)	0.350	0.89 (0.39-2.03)	0.778	1.95 (0.92-4.13)	0.082	1.25 (0.46-3.39)	0.666
Urban v. rural	0.93 (0.68-1.27)	0.638	1.62 (0.93-2.85)	0.090	0.81 (0.47-1.39)	0.638	0.35 (0.13-0.95)	0.039
Social grants/contributions from family members v. formal salary as household income	0.70 (0.49-1.00)	0.047	0.80 (0.42-1.50)	0.478	0.65 (0.36-1.19)	0.162	0.75 (0.30-1.84)	0.524
≤100 v. >100 CD4 at time 1 (cells/mm^3)	1.37 (1.03-1.83)	0.033	0.94 (0.55-1.59)	0.805	2.05 (1.20-3.49)	0.008	1.57 (0.76-3.23)	0.224
Herbs for HIV at baseline v. none	0.73 (0.53-1.00)	0.049	0.47 (0.24-0.92)	0.028	0.94 (0.50-1.78)	0.855	1.01 (0.49-2.07)	0.981
Duration since known HIV-positive								
1995 - 2005	1.00		1.00		1.00		1.00	
2006	0.85 (0.49-1.45)	0.545	0.57 (0.20-1.59)	0.284	1.51 (0.59-3.82)	0.387	0.74 (0.19-2.82)	0.658
2007/8	0.82 (0.58-1.18)	0.289	0.62 (0.34-1.12)	0.113	1.13 (0.55-2.34)	0.743	0.64 (0.27-1.52)	0.312
HIV symptom index at baseline	1.01 (0.99-1.02)	0.404	1.01 (0.98-1.04)	0.563	1.01 (0.98-1.03)	0.625	1.01 (0.97-1.05)	0.590
Depression score at baseline	1.00 (0.98-1.02)	0.713	0.95 (0.91-0.99)	0.016	1.05 (1.01-1.09)	0.009	0.95 (0.89-1.01)	0.074
Hazardous or harmful alcohol use (AUDIT score ≥2)	1.17 (0.69-1.98)	0.562	0.78 (0.25-2.48)	0.676	1.32 (0.54-3.27)	0.544	0.98 (0.22-4.32)	0.984
Health-related quality of life at baseline	0.98 (0.91-1.06)	0.607	1.01 (0.87-1.17)	0.905	0.96 (0.84-1.08)	0.486	0.85 (0.68-1.05)	0.126

[1]Traced living [transferred *N*=58, refused interview *N*=7, treatment denial *N*=8] 73.

A total of 735 patients (217 men and 518 women) prior to initiating ART completed a baseline questionnaire. Extra patients (ARV-naïve) were recruited to increase the initial baseline cohort sample size of 618. Of the 735 patients, 518 (136 men and 382 women) 6 months after initiated onto ART and 557 (158 men and 399 women) 12 months after treatment initiation completed a follow-up questionnaire. Of the 735 patients, 177 (24.1%) were lost to follow-up, 82 (11.2%) died, 58 (7.9%) transferred out of the clinic, 7 (1.0%) refused participation, 8 (1.1%) were not initiated on ART and 22 (3.0%) could not be traced (Fig. 1). From the initially 28 untraceable patients, six were confirmed deceased through verification of vital status from the South African DHA.

Predictors of patients lost to follow-up

Relative risks based on log-binomial regression are reported in Table 2. Being married or cohabitating, not having a formal salary as household income, lower CD4 cell counts, and not using herbal treatments for HIV at baseline were significant predictors of 'loss to follow-up'. Younger age, being married or cohabitating, not using herbal treatments for HIV and lower depression scores at baseline were significant predictors of 'traced living'. Lower CD4 cell counts and lower depression scores at baseline were significant predictors of 'traced deceased' and rural residence at baseline was a significant predictor of 'untraceable'. Sex, age at initiation of ART, marital status, formal education, geolocality, income source, duration since known HIV-positive status, HIV symptoms frequency, health-related quality of life, alcohol use and herbal treatment for HIV at baseline were not associated with death.

Discussion

In this study of 735 patients prior to initiating ART who were followed-up over 12 months in a predominantly rural area in South Africa a total of 24.1% of patients initiating ART were 'lost to follow-up' all-cause attrition (including those who were transferred). Similarly, Fox and Rosen (2010) found a median all-cause adult patient attrition at 12 months of 22.6% (range 7 - 45%) from ART programmes in service delivery settings in sub-Saharan Africa.

We saw a high proportion (46.3%) of mortality. A high rate of mortality (11.2% of participants initiated on ARVs or 46.3% of the lost-to-follow-up participants) happened in the first 6 months of follow-up. Death was also the most common reason for loss to follow-up compared with other reasons, 3.0% were untraceable and 2.1% of participants either were not started on ARVs or refused further participation in the study. Compared with an

urban study from Johannesburg, South Africa, where rate of loss to follow-up and mortality were 16.3% and 5.1% (5.5% were traced living and 5.8% were untraceable), respectively (Dalal *et al.*, 2008). However, in another urban study in Johannesburg of 154 patients' loss to follow-up, a mortality rate of 27% was found (as opposed to 42.6% in this study). Other reasons for loss to follow-up included financial, transport, stopped by doctor, transferred clinics, private medication, social problems, traditional medicine and side-effects (Maskew, MacPhail, Menezes & Rubel, 2007). The high rate of mortality found in this study is still within the high range (20 - 60%) of the meta review by Brinkhof *et al.* (2009) and much higher than in an urban centre, Cape Town, in South Africa, with 6% mortality at 6 months on ART (Boulle *et al.*, 2008). The high early mortality rates indicate that patients are enrolling in ART programmes with far too advanced immunodeficiency. Causes of late access to the ART programme, such as delays in health care access, health system delays, or inappropriate treatment criteria, need to be addressed (Lawn *et al.*, 2006).

The high rate of transfers to other services most likely reflects the local health care system practice of referring patients to the primary health care clinics for follow-up and management. In addition, patients become better in health and go back or migrate to urban centres for work. The traced living group was also younger, which was also found in a cohort study in Cape Town (Van Cutsem *et al.*, 2011). This is important to note, as access to care, both in socio-economic (such as transport) and geographic terms (distance to service) plays an important role in loss-to-follow-up, particularly in rural areas. This seems to be confirmed in this study with the association between rurality and not being traceable among the patients lost-to-follow-up.

Death was the major reason for cohort exit. The study found that the relative risk of death was associated with lower CD4 cell counts and HIV depression scores, which was also found in other studies (Cornell, Myer, Kaplan, Bekker & Wood, 2009; Geng *et al.*, 2009; Hartzell *et al.*, 2008). This finding suggests that treating depression at ART initiation as previously recommended (Jia *et al.*, 2005) may be indicated in this South African population. The results draw attention to the need for early HIV diagnosis, increased access to ART services with earlier treatment initiation, routine screening and aggressive management of opportunistic infections, particularly tuberculosis (Lawn, Harries & Wood, 2010; Macpherson *et al.*, 2008). Differences in health status (lower CD4 cell counts and higher depression scores) should be taken into account when initiating patients on ART.

Limitations

Viral load data were only available for a few participants, and was therefore excluded from the analysis. Furthermore, the assessment of HIV symptoms, quality of life, alcohol use, herbal treatment and other measures relied on self-report. The study results may be biased in favour of those who survived and were healthy enough to participate at follow-up. Sample attrition is a methodological artefact that can potentially influence longitudinal studies (Burgoyne *et al.*, 2004). The findings are derived from a sample of men and women residing in one district in one province in South Africa. Thus caution is urged in generalizing the findings to other districts and provinces in the country. Further, some additional assessments could have been included such as body weight and stage of disease.

Conclusion

Mortality of patient's loss to follow-up was high and occurred early after ART initiation. Differences in health status (lower CD4 cell counts and higher depression scores) should be taken into account when initiating patients on ART. Treating depression at ART initiation is recommended to improve treatment outcome.

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