University of Cape Town

The impact of stressful life events on antiretroviral treatment adherence and viral load amongst adults in Gugulethu, Cape Town

By

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DECLARATION

I, Julie-Anne Coombs, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part thereof has been, is currently being, or is to be submitted for another degree at this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Philosophy in Clinical Research Administration.

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DISSERTATION ABSTRACT

Optimal antiretroviral treatment (ART) adherence is critical in achieving virologic suppression. Most people living with HIV (PLWH) experience HIV-related challenges which may be compounded by the experience of stressful life events (SLE) with adverse effects on their ART adherence and therefore affecting viral suppression. The highest concentration of people living with HIV (PLWH) is in low-and-middle income countries (LMIC) which are challenged with high rates of poverty and unemployment. Limited published data is available on the impact of the stressful life events experienced by PLWH in LMIC on ART adherence and viral load.

A secondary analysis was conducted using data collected in a randomised control trial (RCT) which investigated the impact of a real-time electronic adherence monitoring device (EAMD) on ART adherence in ART-naïve individuals to assess the impact of SLE on ART adherence and viral load.

Part A of this dissertation includes the study proposal/ protocol as approved by the Departmental Research Committee and the Human Research Committee at the University of Cape Town.

Part B details the literature review which examined all published studies which report on stressful life events in PLWH, with ART adherence or a viral load as an outcome. The review included published literature from 2008 to 2019.

Part C includes the publish-ready manuscript which details the statistical analysis, results and interpretation of the secondary analysis of impact of SLEs on ART adherence and viral load among 200 individuals living with HIV.

Part D, appendices were included as supporting documentation necessary for the conduct of this research and as required for the completion of this dissertation.

The American Psychological Association (APA) 6th Edition referencing style was used for Part A and B. The Vancouver referencing style was used for Part C as per the instructions for authors by the Aids and Behaviour journal guidelines.

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Thanks to my husband, Neil and my children Kaylin, Lincoln and Laretia for their patience and for encouraging me to complete this work. A huge debt of gratitude to my husband for stepping in to fulfil all household responsibilities when I had to work on my research.

Finally, I would like to thank the TAP team who did a stunning job in collecting the original data of my research and made it possible to complete to my research.

LIST OF ABBREVIATIONS

ART: Antiretroviral therapy/ treatment

aOR: adjusted odds ratio

EAMD: Electronic Adherence Monitoring Device

HCTC: Hannan Crusaid Treatment Centre, Gugulethu

HIC: High income country

HIV: Human Immunodeficiency Virus

HP-PC: Health Provider pill count

IQR: Inter quantile range

LMIC: Low-and-middle income country

LTFU: Loss to follow-up

OR: Odds ratio

PR: Pharmacy refill

RCT: Randomised Controlled Trial

SD: Standard deviation

SLE: Stressful life event

SR: Self-reporting

TAP study: A randomised controlled **T**rial to explore **A**dherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse **P**harmacokinetic sampling

TDM: Therapeutic Drug Monitoring

USA: United States of America

UTPC: Unannounced telephonic pill count

VF: Virologic failure

VL: Viral load

WHO: World Health Organisation

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PART A: PROTOCOL

1. SYNOPSIS

Title: The impact of stressful life events on adherence and viral suppression among ART naïve individuals

Background and rationale

The introduction of highly active antiretroviral therapy (HAART) more than two decades ago has significantly reduced the mortality and morbidity rates of people living with HIV (PLWH). Generally, PLWH are experiencing better physical health and improved life expectancy that are approaching that of the general population. However, these benefits are largely dependent on effective viral suppression which require almost flawless adherence to antiretroviral treatment (ART). Life-long ART requires life-long adherence.

Previous research has demonstrated that non-adherence to ART is a strong predictor of virologic failure. Virologic failure has life-threatening consequences such as opportunistic infections, disease progression, drug resistance and death.

PLWH are largely concentrated in disadvantaged communities and frequently experience a high degree of stressful life events such as interpersonal violence, injuries, serious illness, housing instability, high levels of crime, difficulties in relationships, finances and employment and death. These stressful life events are associated with missed pills and follow-up appointments.

Therefore, the experience of stressful life events by PLWH can be identified as a barrier to ART adherence.

Aim

This study aims to investigate the impact of stressful life events such as difficulties in health, relationships, work, housing, birth, crime and death experienced by ART naïve individuals over a 48-week period; on their adherence to antiretroviral treatment and virologic suppression. Cumulative adherence was calculated at week 48 "using 3-day self-report (SR), clinic-based pill count (CPC), average adherence by pharmacy refill (PR-average), calculation of medication-free days (PR-gaps), efavirenz therapeutic drug monitoring (TDM) and an electronic adherence monitoring device (EAMD)" (Orrell et al., 2017, p.1).

Objectives

1. To describe the type, frequency and duration of the life events experienced by PLWH.
2. To investigate the impact of stressful life events on antiretroviral treatment adherence and viral load.

Methods and population

This secondary analysis will use retrospective data collected in a randomised control trial (RCT) which investigated the impact of a real-time electronic adherence monitoring device (EAMD) on antiretroviral treatment (ART) adherence in ART-naïve individuals over a 48-week period from 2012 to 2014. 230 HIV-infected individuals, both male and female, participated in this study and attended the Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town. HCTC is a large community-based ART clinic.

The eligibility criteria for the RCT included (1) ART-naive individuals aged ≥15 years old who commenced ART at HCTC; (2) who owned mobile phones; and (3) were able to give

written consent or assent for participants who were ≤18 years old. Participation was offered to all eligible participants who attended the clinic between July 2012 and March 2013.

A Recent Life Event (RLE) questionnaire was administered at week 48 to investigate the contribution of life events to poor ART adherence. The RLE questionnaire included 19 questions on life events in categories such health, death, relationships, work, crime, birth, housing and other life events not mentioned in other categories.

The association between life events and ART adherence and viral load will be determined using logistic regression models to adjust to other covariates that may influence adherence and viral suppression.

2. BACKGROUND

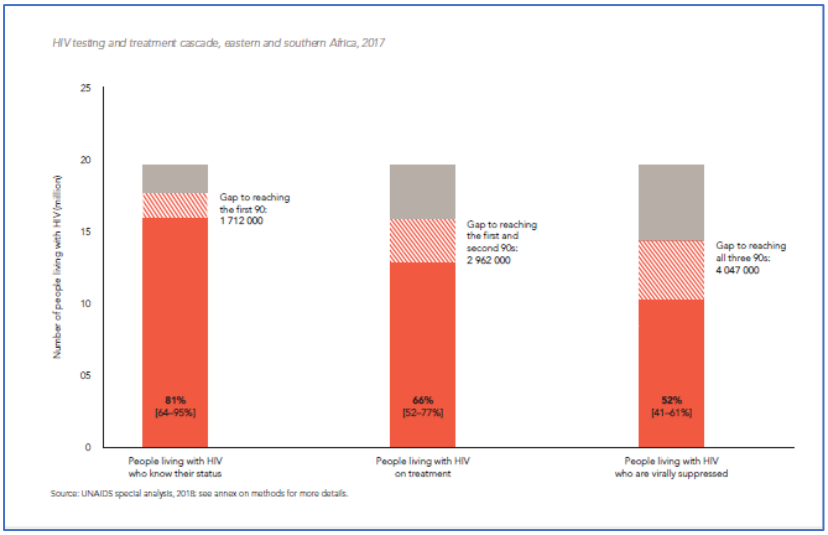
2.1 The disease burden of Human Immunodeficiency Virus (HIV)

The recent 2017 global HIV statistics revealed that HIV continue to be a public health priority (Avert, 2018). Globally, an estimated 36.9 million people were living with HIV which includes an estimated 1.8 million new infections in 2017 with no change to the previous year. More people living with HIV are accessing treatment of which 80% were virally suppressed (Avert, 2018).

In 2014, the World Health Organisation (WHO) set the "90-90-90" target in an attempt to incite further action to achieve the interim 2020 goal which is aligned with the ambitious aim of ending the AIDS epidemic by 2030 (World Health Organization, 2016). "The targets were that: 90% of all people living with HIV will know their HIV status; 90% of all people diagnosed with HIV infection will receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy will achieve viral suppression" (World Health Organization, 2019).

The highest concentration of people living with HIV (PLWH) are living in low-and-middle income countries (LMIC) with an estimated 53% of the world's HIV population located in Eastern and Southern Africa (Joint United Nations Programme on HIV/ Aids (UNAIDS), 2018). South Africa, a Southern African LMIC, has the fourth highest HIV population rate with 13.1% of the general population (Statistics South Africa (Stats SA), 2018). An estimated 7.52 million people living with HIV know their status of which 61% are receiving ART with only 47% who are virally suppressed; a slow progress towards the achievement of the "90-90-90" target (Statistics South Africa (Stats SA), 2018; World Health Organisation, 2019).

Figure 1. HIV testing and treatment cascade- Eastern & Southern Africa, 2017



(Joint United Nations Programme on HIV/ Aids (UNAIDS), 2018)

The expansion of access of ART for all people diagnosed with HIV has significantly reduced the mortality and morbidity rates of PLWH (World Health Organization, 2016). According to the Joint United Nations Programme on HIV/ AIDS (UNAIDS) 2017 global data, 79% of people who knew their HIV status were accessing treatment of which 81% were virally suppressed (Avert, 2018).

2.2 Antiretroviral treatment (ART) non-adherence

Benefits of better physical health and increased life expectancy are largely dependent on effective viral suppression. Currently, there is no official standard measure of adherence to predict successful viral suppression; it is generally accepted that a high level of adherence to ART is required (Betancur, Lins, Oliveira, & Brites, 2017; Parienti et al., 2013). . Author, Schaecher (2013) articulated that, "Different classes of antiretroviral therapy (ArT) are associated with different thresholds of adherence needed to achieve viral suppression and avoid resistance mutations" (p. 231). The challenge of life-long ART is sustaining a high level of adherence (Eshun-Wilson, Rohwer, Hendricks, Oliver, & Garner, 2019)..

Previous research has demonstrated that non-adherence to ART is a strong predictor of virologic failure (Bottonari, Roberts, Ciesla, & Hewitt, 2005) (Schaecher, 2013; World Health Organization, 2016). In the parent study, a randomised control trial (RCT) which investigated the impact of a real-time electronic adherence monitoring device (EAMD) on antiretroviral treatment (ART) adherence in ART-naïve individuals conducted by Orrel et al. (2015), virologic failure was defined as HIV RNA >40 copies/ml. Virologic failure has life-threatening consequences such as opportunistic infections, disease progression, drug resistance and death, as well as risk of transmission of HIV to sexual partners and unborn children (Betancur et al., 2017; Corless et al., 2017; Mutumba et al., 2016).

2.3 Stressful life events as a barrier to ART adherence

In South Africa, the majority of PLWH live in disadvantaged communities and frequently experience HIV-related challenges such as stigmatisation and discrimination which may be compounded by the experience of stressful life events such as interpersonal violence, psychological disorders, injuries, serious illness, housing instability, high levels of crime, difficulties in relationships, finances and employment; and death (Azia, Mukumbang, & Van Wyk, 2016; Kalichman & Kalichman, 2016; O'Donnell et al., 2017). These challenges are typical barriers to ART adherence and are associated with missed pills and follow-up appointments(Azia et al., 2016; O'Donnell et al., 2017; Weinstein & Li, 2016).

3. HYPOTHESIS

The experience of stressful life events by people living with HIV will adversely impact their adherence to antiretroviral treatment and therefore affect virologic suppression.

4. PROBLEM STATEMENT

In South Africa, widespread poor adherence to ART has resulted in a population-wide risk of poor viral suppression, development of drug resistance, loss to care and increased mortality. Therefore, barriers to adherence in specific communities need to be identified and addressed with appropriate strategies.

5. OBJECTIVES

5. To describe the type and frequency of the life events experienced by PLWH in Gugulethu community in Cape Town, over a 48-week period
6. To investigate the impact of these stressful life events on antiretroviral treatment adherence and viral load, measured over a 48-week period.

6. METHODS AND POPULATION

This secondary analysis will use retrospective data collected in a randomised control trial (RCT), previously approved by University of Cape Town Human Research Ethics Committee (UCT HREC) with reference 158/ 2012, which investigated the impact of a real-time electronic adherence monitoring device (EAMD) on antiretroviral treatment (ART) adherence in ART-naïve individuals over a 48- week period from 2012 to 2014.

230 HIV-infected individuals, both male and female, participated in this study and attended the Hannan Crusaid Treatment Centre (HCTC) in Gugulethu, Cape Town. HCTC is a large community-based ART clinic (Orrell et al., 2015).

The eligibility criteria for the RCT included (1) ART-naive individuals aged ≥15 years old who commenced ART at HCTC; (2) who owned mobile phones; and (3) were able to give

written consent or assent for participants who were ≤18 years old. Participation was offered to all eligible participants who attended the clinic between July 2012 and March 2013 (Orrell et al., 2015). A simple random sampling strategy was used. "Participants were randomized 1:1 to control and intervention arms. Allocation to study arm was concealed in sealed individual opaque envelopes, which were numbered from 1 to 230 and opened consecutively after a participant met study entry criteria. The random number sequence and envelopes were generated off-site. The envelopes were opened by the study nurse, blinded to the allocation, onsite. Staff (both study and clinic) and participants were not masked to arm allocation after randomization"(Orrell et al., 2015, p. 497).A Recent Life Event (RLE) questionnaire (Appendix 1) was administered at week 48 to investigate the contribution of life events to poor ART adherence. The RLE questionnaire included 19 questions on life events in eight categories such health, death, relationships, work, crime, birth, housing and other life events not mentioned in other categories. A binary life event variable will be created, defined as any life event experienced versus non-experienced. A continuous variable of frequency (count) of life events will also be assessed.

Other psychosocial covariates measured in the parent study were anxiety and depression using a 14-question Hospital Anxiety and Depression Score (HADS) (Appendix 2) and alcohol abuse assessed using a four question CAGE score (Appendix 3) (Orrell et al., 2015).

Depression and anxiety cases were identified using a cut-off score of ≥ 8 for depression and ≥ 8 for anxiety. Cases of alcohol abuse were identified using a cut-off score of ≥2.

Cumulative ART adherence was measured using an electronic adherence monitoring device (EAMD, Wisepill®) and "calculated by the number of days the container was opened over the number of days in the period in care…" (Orrell et al., 2015, p. 498).

Further, to examine the cumulative adherence data and HIV RNA levels: a level of ≥90% of the number of pills taken will be considered as adherent and virologic failure will be recorded when the HIV RNA levels is ≥ 40 copies/ millilitre.

7. DATA ANALYSIS

The existing data was cleaned and evaluated using the STATA statistical package version 13.0. Further data analysis for this study will be analysed using the same statistical package.

Descriptive statistics will be used to summarise the baseline demographics, adherence, VL measures and psychosocial measures, which will include means, standard deviations, medians and interquartile ranges on continuous data and percentages on categorical data as well as tabulate the life events data.

Multivariate logistic regression analysis will be used to explore associations between adherence and life events, and between VL and life events. Life events will be assessed in separate models as binary variable and as continuous variable of frequency of events. Impact of potential confounders will be assessed in these models. Confounders of interest include age, gender, depression (binary), anxiety (binary) and alcohol abuse (binary). Collinearity between anxiety and depression will also be assessed.

Of the eight life event categories assessed, the most common life events may be assessed in separate logistic regression models.

8. LIMITATIONS

The study is limited in its generalizability. The study sample was from a disadvantaged community with a high rate of unemployment and representativeness for all PLWH cannot be assumed. Selection bias could have occurred due to the number of unemployed participants being more available to participate in the study. Participants enrolled in the index study received additional adherence support more than would be expected during routine clinic visits. Weinstein and Li (2016) found that researchers conceptualized stress experienced by PLWH in different ways and the current study was limited by the categories of stressful life events investigated and cannot be considered exhaustive. Although, the study will control for confounding of other psychosocial variables, which are known to influence medication adherence, we cannot exclude the influence of other factors on medication adherence. Another limitation of the study is that the Recent Life Event Questionnaire was administered at the end of the index study and therefore, data will only be available for the 186 participants who completed the study. However, there is evidence for the importance of considering the impact of stressful life events on ART adherence and the need to implement interventions to alleviate stress in PLWH.

9. PRESENTATION AND DISSEMINATION OF RESULTS

A minor dissertation will be submitted in fulfilment of the requirement for the Master of Philosophy in Clinical Research Administration degree as per the University of Cape Town guidelines.

10. FEASIBILITY AND ETHICAL CONSIDERATIONS

Minimal resources will be required for this study. Retrospective data for the secondary analysis will be provided by the author of the index study, Associate Professor Catherine Orrell.

10.1 Ethical considerations

The proposed study is a secondary analysis based on retrospective data collected in a clinical trial previously approved by the Human Research Ethics Committee of the University of Cape Town: HREC Ref no: 158/2012. University of Cape Town HREC approval for the Recent Life Event (RLE) questionnaire is attached (Appendix 4).

10.2 Informed consent

In accordance with ethical standards, written informed consent was obtained from each participant before enrolment into the index study. No further informed consent will be required for this research and therefore, participants will not be contacted.

10.3 Risk and benefits to participants

There are no risks and no direct benefits to the participants.

10.4 Confidentiality and privacy

Only de-identified data in the form of code numbers will be shared with no linkage to participants' personal details. Participant anonymity will be maintained throughout the research

10.5 Data protection and storage

All data are anonymised and are stored on a password-protected computer. Access will be limited to the researcher. Only encrypted data will be shared.

11. RESEARCH TIMELINES

Planned activity	Timelines
DREC Submission & Approval	May – Aug 2019
FHS HREC Submission	Sep 2019
FHS HREC approval	Sep 2019
Data Analysis	Oct2019
First Draft of Dissertation	Oct 2019
Final dissertation	Nov 2019
Dissertation submission	Dec 2019

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PART B: STRUCTURED LITERATURE REVIEW

1. INTRODUCTION

Optimal antiretroviral treatment (ART) adherence is critical in achieving virologic suppression. ART adherence is used in the assessment of progress towards the 90-90-90 World Health Organisation global challenge which includes achieving 90% viral suppression for all people living with HIV (PLWH) who are on treatment (World Health Organization, 2016). Constant monitoring of ART adherence is required to achieve this goal. The expansion of access of ART in developing countries has significantly increased the life expectancy of PLWH (Masquelier & Reniers, 2018). The growing challenges are maintaining optimal adherence on lifelong ART, retention in care and achieving viral suppression (World Health Organization, 2016). The Sub-Saharan African region carries the highest burden of HIV infection world-wide (53%), with an estimation of 25.7 million PLWH (Joint United Nations Programme on HIV/ Aids (UNAIDS), 2018). The majority of PLWH live in resource-poor countries and their lives are complicated by poverty and HIV-related, as well as life-related stressors. Identification of barriers to ART adherence, including such life stressors, particularly in this context, is important in developing support strategies and differentiated care models (Azia, Mukumbang, & Van Wyk, 2016; Nachega, Sam-Agudu, Mofenson, Schechter, & Mellors, 2018).

This literature review aims to examine all published studies which report on stressful life events in PLWH, with ART adherence or a viral load as an outcome. This review will include published literature from 2008 to 2019 and will include both resource-poor and resource-rich contexts with no differentiation in study design.

2. OBJECTIVES OF THIS LITERATURE REVIEW ARE TO REPORT

- Stressful life events (SLEs) in PLWH
- Covariates associated with poor adherence
- Measures of ART adherence and virologic outcomes

3. LITERATURE SEARCH STRATEGY

A search for published studies was conducted using the following databases: Pubmed, MEDLINE, Google Scholar, CINAHL, PsycINFO and SCOPUS. A combination of key words and Medical Sub-headings such as "HIV OR human immunodeficiency virus" AND "stressful life events OR life events OR life change events" AND "antiretroviral therapy" AND "adherence OR compliance" were used to obtain relevant literature. Limiters applied in this search were full text and peer-reviewed articles in the English language with age restricted to adults of 18 years and older. To be included, the literature had to identify "stressful life events OR life events" as exposure variable and "ART adherence or viral load" as an outcome variable.

4. RESULTS OF LITERATURE SEARCH

The search generated 24 articles of which only 12 met the inclusion criteria. Among these studies, 9 studies were conducted in a high-income country (HIC), one in a lower-middle income country (LMIC) and two studies included sites from both HIC and LMIC. HIC and LMIC are classified by the World bank according to the country's income level (World Bank). The 9 studies from HICs included: 7 from the US and 1 study from Australia and 1

study which included 4 HIC sites (Table 1). The only LMIC study was from South Africa. Two studies conducted by Corless et al. (2013 & 2017) included sites from both, HIC (Canada, US, Puerto Rico) and LMIC (Namibia, Thailand, China). One systematic review conducted by Weinstein et al. (2016) was included. The systematic review examined the link between stress and treatment adherence, immunological outcomes, virologic outcomes and disease progression; in the selected literature. Studies mentioned in this literature review were not mentioned in the systematic review. Nine studies reported on adherence as a primary outcome, one study reported a virologic outcome and two reported both an adherence and virologic outcome.

4.1 Stressful life events (SLEs) in people living with HIV (PLWH)

SLEs can cause major disruption in the lives of PLWH resulting in negative adherence behaviour and poor health outcomes (O'Donnell et al., 2017). PLWH and living in poverty have added challenges contributing to increased non-adherence. SLEs have been described in various ways such as HIV-related stressors, non-HIV related stressors, life experiences, psychological stressors or biological markers linked to stress (Weinstein & Li, 2016). The impact of SLEs on ART adherence may depend on the number of events experienced and/ or the type of SLEs. Studies varied in stress measures used, prevalence rates and common stressful life events.

4.1.1 Stressful life event measures

Various validated self-reporting stress measures were used across the 12 studies. Weinstein et al. (2016) reported findings of 22 different measures that were used across 23 studies. The

57-item Life Experiences Survey (LES) developed by Saranson et al. (1978) was modified, validated and commonly used in four studies (Leserman, Ironson, O'Cleirigh, Fordiani, & Balbin, 2008; Mugavero et al., 2009; O'Donnell et al., 2017; Reif et al., 2011). The LES captured moderate and severe stressful life experiences such as relationship difficulties, death or serious illness, financial problems, employment difficulties, legal problems, sexual or physical abuse and housing difficulties. Other studies used scales previously developed and validated which were typically used in studies of mental health in PLWH (Brinkley-Rubinstein, Chadwick, & Graci, 2013; Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016; Siefried et al., 2017). Corless et al. (2013 & 2017) developed and used a 20-item Stressful Life Event Questionnaire modified from the List of Threatening Experiences Questionnaire [LTE-Q; (Brugha & Cragg, 1990)] which measured similar experiences of SLEs such as death or serious illness, injury, unemployment and stigma. Bottonari et al. (2010), differentiated between chronic, acute and perceived stress using the Chronic Strain Interview [CSI; (Hammen et al., 1987)], the Life events and difficulties schedule [LEDS; (Brown, 1989)] and the Perceived stress scale-4 item version [PSS; (Cohen, 1988)], respectively.

4.1.2 Prevalence of SLEs

Nine of the 12 studies reported the high prevalence of SLEs and their association with a negative adherence outcome. In two studies, based on data from the Coping with HIV/ AIDS in the Southeast (CHASE) study, Mugavero et al. (2009) reported medians of nine incident stressful events including three incident severely stressful events over a two-year period, and Reif et al. (2011) reported medians of three stressful experiences and one severely stressful experience over a nine-month period. Two studies, conducted by Kalichman et al. (2010 & 2016), found a higher number of SLEs experienced by the non-adherent group compared to

the adherent group, i.e means of 4.3-4.7 vs 3.5. Both, Corless et al. (2013) and Bottonari et al. (2010) found a mean of 5.6 SLEs experienced by the total study sample over one month. Other studies reported a mean of 2-3 SLEs measured over different periods (Leserman et al., 2008; O'Donnell et al., 2017; Siefried et al., 2017).

4.1.3 Common Stressful life events

Findings of the most common stressful life events within the study sample differed among the studies. Ongoing financial stressors, serious illness or death of a partner, friend or family member and unemployment ranked the highest across most studies (Table 2). Some studies mentioned relationship difficulties, food insecurity, housing instability, lack of transport, safety issues and legal problems as high-ranking stressors (Bottonari, Safren, McQuaid, Hsiao, & Roberts, 2010; Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016; Leserman et al., 2008; Mugavero et al., 2009; O'Donnell et al., 2017; Reif et al., 2011).

Eleven of the studies described the SLE experiences of PLWH in HIC and may not be generalizable to PLWH in resource-limited settings, however it gives an indication that populations living in resource-limited settings may be at higher risk of increased SLEs and chronic stress which may impact their ability to maintain optimal adherence.

4.2 Covariates associated with poor adherence

All studies included numerous psychosocial measurements given the significance of these variables in the prediction of medication adherence. Confounding factors examined in the literature were: depression, alcohol and drug use, anxiety, HIV care self-efficacy, coping

styles, HIV status disclosure, stigma, quality of life of PLWH, self-esteem, sense of coherence, self-compassion, poverty experiences, life chaos and adult literacy.

Depression was reported in eleven studies using various validated scales. Commonly used scales were: the Center for Epidemiological Studies-Depression Scale [CES-D; (Radloff, 1977)], the Brief Symptoms Inventory measured depression and anxiety [BSI; (Derogatis & Melisaratos, 1983)], the Beck Depression Inventory [BDI; (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)], the Hamilton Depression Rating Scale [HDRS; (Hamilton, 1960)] and the Montgomery-Asberg Depression Rating Scale [MADRAS; (Montgomery & Asberg, 1979)]. Weinstein et al. (2016), reported the Hospital Anxiety and Depression Scale [(HADS; (Zigmond & Snaith, 1983)] that was used in two studies. Brinkley-Rubinstein et al. (2013) reported mental health notations from medical notes.

Alcohol and drug use was assessed in seven studies: Siefried and colleagues (2017) used the 'Cut-Annoyed-Guilty-Eye' questionnaire [CAGE; (Ewing, 1984)]; Kalichman et al. (2010 & 2016) used the Alcohol Use Disorders Identification Test [AUDIT; (Maisto, Conigliaro, McNeil, Kraemer, & Kelley, 2000)] in two studies; both, Reif et al. (2017) and Mugavero et al. (2009) used the Addiction Severity Index [ASI;(Cacciola, Alterman, McLellan, Lin, & Lynch, 2007)]; and O'Donnell et al. (2017) reported using the Mini International Neuropsychiatric Interview [MINI; (Lecrubier et al., 1997)] to assess alcohol and drug use. Health behaviours such as alcohol use and cigarette smoking were examined by Leserman et al. (2008) in less detail.

Based on evidence indicating the negative influence of SLEs on the overall quality of life of PLWH; Corless et al. (2013 & 2017) uniquely examined the sense of coherence, self-

compassion, adherence self-efficacy and the engagement with healthcare providers as mediators of SLEs on ARV adherence and found these combined variables were significant predictors of adherence. Adherence self-efficacy which "measures the confidence of the respondent in completing treatment-associated behaviours and incorporating those behaviors into daily life as appropriate"; was found to be the strongest predictor of ART adherence in this study (Corless et al., 2017, p. 229).

Despite major advances in the acceptability of ART and the escalation to ART access, PLWH continue to face challenges of disclosure, stigma and discrimination which impede the uptake of treatment as well as maintaining adequate ART adherence. Some HIV populations experience increased vulnerability, particularly girls and women in Sub-Saharan Africa, who are exposed to gender-inequality and gender-based and sexual violence (World Health Organization, 2016). The focus is therefore for healthcare systems to create an enabling environment by developing policies and practices that would address stigma and discrimination and encourage disclosure among PLWH. Six studies reported stigma and discrimination as additive stressors to adherence using self-reporting questionnaires with findings consistent with previous research which found stigma and discrimination as strong predictors of non-adherence (Corless et al., 2013; Corless et al., 2017; Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016; O'Donnell et al., 2017; Siefried et al., 2017). Siefried et al. (2017), found more than 40% of the cohort reported to be shamed, blamed and/ or rejected or excluded after disclosing their HIV status.

Coping styles were examined in four studies using the Brief Cope instrument (Carver, 1997) to determine the mediating effect of maladaptive coping on the relationship between SLEs and adherence (Bottonari et al., 2010; Mugavero et al., 2009; O'Donnell et al., 2017; Reif et

al., 2011). Mugavero et al. (2009) and Reif et al. (2011) used similar definitions of coping styles; forming two scales of adaptive (positive reframing, using emotional support, acceptance, religion, active) and maladaptive (denial, self-blame, and behavioural disengagement) coping styles. Bottonari et al. (2010) broadened the dimensions of coping by using two factors which consisted of: "Active coping" (emotional support, instrumental support, planning, positive reframing, humor, acceptance, and religion) and "Avoidant coping" (denial, substance use, behavioral disengagement, venting, and self-blame). Although Reif et al. (2011) found maladaptive coping to be associated with stressful experiences, other studies reported SLEs predicted non-adherence after adjusting for covariates such as coping styles (Bottonari et al., 2010; Mugavero et al., 2009; O'Donnell et al., 2017).

Kalichman et al. (2010 & 2016) examined the link between poverty markers (food and housing insecurity) and ART adherence with stressors and life-chaos as mediators; the studies also reported stressors (social, health-related and HIV-related) and life chaos as predictors of non-adherence. Further findings reported in these studies were: food insufficiency and hunger as a strong predictor of non-adherence in a low-literacy study population and the addition of stressors and chaos as mediators resulted in a non-significant association between poverty markers and ART adherence. These studies reported the need to address food insufficiency together with interventions to manage stress in PLWH, particularly in disadvantaged populations, to improve ART adherence.

4.3 Measure of ART adherence

Medication adherence is defined as the extent to which a person correctly takes the medication as prescribed by the healthcare provider (Nachega, Mills, & Schechter, 2010).

Previous literature suggested various adherence levels of 70% to ≥95% to achieve virologic suppression (Nachega et al., 2010). Adherence is defined in various ways in the selected literature: four studies, using self-reporting measures, defined non-adherence as missed doses over the past 7 days, past 2 weeks, past 30 days and the previous weekend (Bottonari et al., 2010; Leserman et al., 2008; Mugavero et al., 2009; Siefried et al., 2017); and four studies defined adherence as more than 85 -90% of pills taken over a specified period (Brinkley-Rubinstein et al., 2013; Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016; O'Donnell et al., 2017). Adherence was not defined in three of the studies (Corless et al., 2013; Corless et al., 2017; Weinstein & Li, 2016).

Multiple measures to estimate adherence are reported in published literature. Methods used can be direct such as therapeutic drug monitoring (TDM) which measures the level of the last dose of the drug taken or indirect methods such as self-reporting (SR), clinic-based pill counts (CPC), pharmacy-refills (PR) or electronic adherence monitoring (EAM) (Glass & Cavassini, 2014; Orrell et al., 2017). Although adherence thresholds to predict treatment success remains undefined; a high level of adherence is reportedly accepted as determinant of optimal viral and immunological outcomes. SR, CPC and PR are commonly used in clinical care in resource-limited settings. Although these methods are often inaccurate and overestimate adherence, they are the most accessible and feasible measures of adherence to collect (Orrell et al., 2017). There is no single optimal measure of adherence; therefore, using a multi-method approach is more likely to provide an accurate measure of adherence behaviour (Glass & Cavassini, 2014). In this review, seven studies reported a self-reporting method, three studies used an unannounced telephonic pill-count method and one reported a clinician pill count.

SR measures are low-cost and convenient; but are largely subjected to recall bias and intentional deception due to social desirability bias (Glass & Cavassini, 2014). Using validated SR instruments allows for assessment of four dimensions of adherence behaviour: assessment of number of pills taken, timing compliance, missed doses and food intake (Glass & Cavassini, 2014). Validated SR instruments were used in six studies: two studies used a 30-day Visual Analog Scale for medication adherence [one-item scale adapted from MASRI scale;(Walsh, Mandalia, & Gazzard, 2002)]; three studies used a modified version of the Adult AIDS Clinical Trial Group instrument [AACTG: (Chesney et al., 2000)] and one study used a Simplified Medication Adherence Questionnaire [SMAQ:(Knobel et al., 2002)] (Bottonari et al., 2010; Corless et al., 2013; Corless et al., 2017; Leserman et al., 2008; Mugavero et al., 2009; Siefried et al., 2017). Using the 30-day Visual Analog Scale, participants had to indicate on a scale of 0% to 100% the amount of time they have taken their medication as prescribed. The questionnaires interrogated medication adherence using responses to number of pills taken and missed doses over a specified period. O'Donnell and colleagues (2017) reported a self-reporting method using a telephonic structured interview to record responses to questions on pills taken and missed doses over the previous month. Periods of measurement or recall varied from the past 7 days up to the past 30 days. Short recall periods of 3 to 7 days have been suggested in several studies to maximise recall and minimise bias (Lu et al., 2008). Recent evidence suggests that longer recall periods of 30 days and including the previous weekend may be more optimal in measuring missed doses and in determining patterns of adherence behaviour (Lu et al., 2008; Walsh et al., 2002).

Kalichman et al. (2010 & 2016) and O'Donnell et al. (2017) reported an unannounced telephonic pill count-method to assess medication adherence. In previous research, Kalichman and colleagues (2007) found this method in assessing medication adherence to be

reliable and valid when followed-up with unannounced home visits to repeat pill counts. Unannounced telephonic pill counts were performed at various intervals in the three studies: once a month, at 12-16 day- or at 21-35 day-intervals.

Brinkley-Rubinstein et al. (2013) reported adherence based on clinician pill counts notated in medical charts. Adherence lapses were noted when adherence was reduced to less than 90%. The systematic review reported the measurement of ARV adherence in eleven studies; methods were unspecified (Weinstein & Li, 2016). Three studies reported >1 adherence measure: Siefried et al. (2017) and Kalichman et al. (2010) reported pharmacy refills as additional adherence measure and O' Donnell et al. (2017) used a self-reporting measure as well as unannounced telephonic pill-count.

Nine of the 11 studies which assessed adherence reported proportions of adherent participants ranging from 33-96%. Estimates from two studies using unannounced telephonic pill-counts (calls at 12-16 day- or at 21-35 day-intervals) with a cut-off of 85% reported proportions of adherence of 33% and 47%, respectively (Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016); compared to another study using the same adherence measure with monthly calls and a cut-off of 95% which reported a median adherence of 96% (O'Donnell et al., 2017).

4.4 Virologic outcome

HIV RNA results were selected from a medical record abstraction in five studies, one study measured viral load at baseline and one systematic review reported virologic outcomes in 12 studies (Bottonari et al., 2010; Kalichman & Grebler, 2010; Kalichman & Kalichman, 2016; Leserman et al., 2008; Mugavero et al., 2009; Reif et al., 2011; Weinstein & Li, 2016).

Virologic failure (VF) was defined in three studies: Bottonari et al. (2010) defined VF as HIV RNA levels as >50 copies/ ml and both, Mugavero et al. (2009) and Reif et al. (2011) defined VF as HIV RNA levels >400 copies/ ml. The proportion of virally suppressed participants varied across four studies ranging from 46 – 71% and proportions were not reported in three studies (Kalichman et al., 2010 & 2016; Reif et al. 2011; Bottonari et al., 2010). Kalichman et al. (2010) reported viral suppression of 72% in a non-adherent group at a threshold of 85% adherence with an overall of 71% of the cohort that were virally suppressed. Leserman et al. (2008) measured HIV RNA at baseline with no report of the results of this measurement. Poor adherence was not reported to be associated with poor virologic outcomes in any of the studies.

4.5 Stressful life events (SLEs) as predictor of adherence and virologic outcome

SLEs were reported to be consistently associated with non-adherence or missed pills in the eleven studies which reported an estimation of adherence. A high number of SLEs were associated with non-adherence and the addition of one SLE predicted the deterioration of ART adherence.

Weinstein et al. (2016) reported 12 studies in the systemic review which measured virologic outcomes, four of the studies found SLEs to be associated with VF and eight studies found no significant relationship between SLEs and VF. Reif et al. (2011) also found no association between SLEs and VF; in contrast, Mugavero et al. (2009) reported a significant association between these variables.

5. STUDY RATIONALE

There is a paucity of literature on stressful life events in PLWH and its impact on ART adherence and virologic outcomes in LMIC, particularly in South African context. Although some of these stressful experiences in PLWH have been reported in a recent South African study with encouraging findings, the number of stressful life events assessed were limited. While published studies in developed countries, indicated significant associations between SLEs and adherence and/ or viral load, comparability was limited by the different methods used to assess SLEs and adherence as well as the different definitions and thresholds of adherence and virologic outcomes. To increase understanding of the impact on SLEs on adherence in a LMIC, an assessment of a comprehensive range of potential stressful life experiences using multiple measures of adherence validated with viral load, are needed. This study aims to provide information on SLEs in PLWH and adherence and virologic outcomes, using an electronic monitoring adherence measure and viral loads.

Table I. Characteristics of studies

Authors	Year Published	Location	Time	Study design	Study population
Siefried et al.	2017	Australia	Sep 2013-Nov 2015	Cross-sectional study of a baseline sample	522 -virally suppressed at baseline Males=494 (94.6%) Mean age 50.8 years
O'Donnell et al.	2017	USA (North Carolina)	Jul 2011- Sep 2013	Secondary analysis - data from a RCT 12 month follow-up	289-clinically depressed participants -Male (71%) Median age of 45 years.
Corless et al.	2017	Canada, Namibia, Thailand, United States, Commonwealth of Puerto Rico	Not reported	Cross-sectional study	1811 -Males (71%)
Weinstein and Li	2016	USA, The Gambia, Spain, Hong Kong	Published articles between 1995 and 2012.	Systematic review	23 articles
Kalichman & Kalichman	2016	USA (Georgia)	Dec 2013- Mar 2014	Observational study – 6-week prospective period	92 -Male (83.6%)
Brinkley-Rubinstein et al.	2013	South Africa (Western Cape)	Not reported	Systematic, retroactive review of medical charts	171 - Males (28%) Mean age of 39 years
Corless et al.	2013	USA (14 sites), Canada (1 site), China (1 site), Namibia (1 site), Puerto Rico (1 site), Thailand (1 site)	Sep 2009 - Jan 2011	Multi-site cross-sectional investigation	2082 -Males (68.3%; n=1404) Mean age of 44.9 years
Reif et al.	2011	USA (South-eastern states)	Dec 2001- Apr 2002	Secondary analysis	611 (589 surveyed)- Males (69%) Mean age of 40.1 years
Kalichman and Grebler	2010	USA (Georgia)	Oct 2008-Aug 2009	Prospective study - 3 months duration	188 poor literacy -Males (69.1%) Mean age of 46.7 years
Bottonari et al.	2010	USA	Not reported	Prospective study - baseline & 3-month follow-up	87 - Males (54%) Mean age 46 years
Mugavero et al.	2009	USA (South-eastern states)	2001-2002	Prospective study- follow-up over 27 months in an 8-site, 5-state study	474 at baseline - Males 71% 289 at 27-month follow-up Median age of 40 years
Leserman et al.	2008	USA (South Florida)	2004-2007	Cross-sectional study	105 - Male= 61% Mean age 44

Table II. Stressors, Covariates, Adherence and Virologic outcomes

Authors	Most common stressors	Number of events	Covariates	Adherence definition	*Method	Adherence outcome	Virologic outcomes
Siefried et al. (2017)	Financial difficulties Unemployment Living in subsidized housing	Experienced >2 major stress events in previous 12 months (25.5%)	Depression Alcohol and illicit drug use HIV disclosure Stigma	Missed one dose per month	SR, PR	78 participants (14.9%) reported missing doses. Socioeconomic, cultural, social, relationship, and patient engagement factors associated to suboptimal adherence	Not reported
O'Donnell et al. (2017)	Financial difficulties illness/ injury/ hospitalization Death/serious illness of family member/friend	Median of 2 events per month	Depression HIV care self-efficacy Coping style HIV-related physical symptoms HIV status disclosure Employment status Drug and/or alcohol abuse.	Adherence >95%	UTPC, SR	Median monthly adherence 96% SR at baseline -median of 98% Pill count-measured median 96% Greater number of past-month SLEs was associated with poorer past-month ARV adherence	Not reported
Corless et al. (2017)	Not specified	Not specified	Engagement with HCP, Self-esteem, Perceived stigma, Sense of coherence, HIV adherence self-efficacy, Self-compassion, Depression, Anxiety	None (0%), Low (1–60%), Moderate (61–94%), and High (95–100%)	SR	High (95–100%) -52.3% Medium (61–94%) - 33.3% Low (1–60%) - 8.3% None - 6% Stressful life events were significant predictors of medication adherence.	Not reported
Weinstein and Li (2016)	Not specified	Not specified	Anxiety Depression	Not reported	Not reported	Adherence was measured in 11 studies. Higher stress was found to be related to poorer treatment adherence in 5 studies (22%) and not significant in 6 studies.	Viral load measured in 12 studies (52%) Stress was related to higher viral load in four studies (17%)
Kalichman & Kalichman (2016)	Unemployment Food insecurity Lack of transportation Housing instability	HIV related stressors: Adherence <85%= mean 4.7 Adherence >85%)= mean 3.5 Poverty markers: Adherence <85% =mean 4.7 Adherence >85% = mean 4.1	Alcohol use Depression Life chaos HIV-related stressors (stigma, discrimination, disclosure)	Adherence >85%	UTPC	Non-adherence 54% (n=50) Life chaos with HIV-related stressors, is associated with both non-adherence and poverty.	29% were not HIV virally suppressed

Brinkley-Rubinstein et al. (2013)	Death or illness of friend or family member	Not specified	Mental health notations	Adherence >90%	HP-PC	Non-adherence 47% (n=81), Serious life event was significantly associated with anti-retroviral adherence lapse and mental health issues.	Not reported
Corless et al. (2013)	Unemployed (75%)	SLEs mean 5.69 (SD=4.88) and 89% of the sample had at least one SLE.	Sense of Coherence Self Compassion Engagement with Healthcare Provider Stigma	Not reported	SR	Canadian: 3 days (M=86.49) or 30 days (M=84.12); Namibian:3 days (M=96.21) or 30 days (M=95.81). SLE, SCS, SOC, and eHCP were significant predictors of adherence	Not reported
Reif et al. (2011)	Financial stress Major illness or injury Death of family member or close friend Relationship difficulties Employment difficulties	Incident stressful experiences - median 3.5 experiences and 10% of study participants reported traumatic stress in any given nine-month period	Depression Alcohol and drug use Post-traumatic stress disorder Coping styles	Not reported	Not reported	Not reported	VL<400cps/ml = 237 (46.1%) Viral load was not associated with stressful experiences.
Kalichman and Grebler (2010)	Food insecurity Unemployment Relationship difficulties	Total stressors: Adherence >85% = 3.5 Adherence <85% = 4.3	Neurocognitive dysfunction Depression Stigma Alcohol and substance use	Adherence >85%	UTPC, PR	Non-adherence 67% (n=127) Social and health-related stressors were associated with ART adherence.	**Undetectable VL:** <85% = 92/ 127 (72.4%) >85% = 42/ 61 (68.9%) Total = 134/ 188 (71.3%)
Bottonari et al. (2010)	Relationship difficulties Housing instability Unemployment Serious illness among family members	Measured at baseline (T1) and at 3-month follow-up (T2) Life stress T2 LEDS = 5.6 T2 CSI = 13.6 T2 PSS = 6.7	Adult literacy Brief Cope inventory Depression Major Depressive Episode (MDE)	Number of missed doses in the past 30 days	SR	47% (n = 41) reported 100% adherence at either 3- or 30- day assessment and 33% (n = 29) reported perfect adherence for both periods. Acute life events and chronic stress prospectively predicted decreases in treatment adherence	Virologic failure defined as HIV VL > 50cps/ ml Undetectable viral loads = 62%
Mugavero et al. (2009)	Financial difficulties Serious injury or illness Death of a family member or close friend Employment-related stressors Safety-related stressors.	Median of 9 incident stressful events, including 3 incident severely stressful events	Depression Alcohol and drug use Coping styles	Missed doses during the past 7 days;	SR	Relationship, safety-related, and life transition stresses were associated with decreased adherence Non-adherence (n=60) 21%	Virologic failure defined as HIV VL >400cps/ ml Relationship stresses and injuries, accidents, and non-HIV related illnesses predicted virologic failure

Leserman et al. (2008)	Chronic financial difficulties Relationship difficulties - arguments, separation, estrangement Serious illness or injury Unemployment Death of close friend or family member	Median 3 events	Depression Alcohol and substance use	Missed doses in the past 2 weeks or previous weekend	SR	44.8% had missed a medication dose in the past 2 weeks, and 22.1% had missed their medication during the previous weekend. Stressful life events were consistently associated with missing HIV medication	Blood draw at baseline- CD4 and HIV RNA viral load.

*Methods: Unannounced Telephonic Pill-counts (UTPC), Self-reporting (SR), Health Provider Pill-count (HP-PC), Pharmacy Refills (PR)

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PART C: JOURNAL MANUSCRIPT

The impact of stressful life events on ART adherence and viral load amongst adults in Gugulethu, Cape Town

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ABSTRACT

People living with HIV (PLWH) experience HIV-related challenges which may be compounded by the experience of stressful life events (SLE), impacting their ART adherence and affect virologic outcome.

A secondary data analysis was conducted to examine the impact of SLE on ART adherence and viral load among ARV-naïve individuals. A recent life event questionnaire was administered including life events in eight categories: health, death, relationships, work, crime, birth, housing and other.

200 participants completed the questionnaire. 67,5% were female, with a median age of 32.7 (IQR 27.4-41.1) years. A total number of 353 life events were recorded, a median of 1.0 (IQR 0-3) SLEs per person. A significant association was found between the total number of events experienced and virologic failure (OR 1.3, CI 1.06 -1.60, p=0.011). Age was protective (aOR 0.92, CI 0.85-0.99, p=0.042). Poor birth outcomes (a personal or household experience of a miscarriage, termination of pregnancy or still birth) were strongly associated with poor adherence (aOR 6.45, CI 1.25-33.29, p=0.026) and virologic failure (aOR 8.88, CI 1.56-50.58, p=0.014).

People with multiple SLEs, including poor birth outcomes, and younger individuals, are at higher risk of virologic failure and/or poor adherence. These associations highlight the need for differentiated care models; providing focussed support for younger PLWH, pregnant and postpartum women.

Keywords: Human Immunodeficiency Virus (HIV), Stressful life events (SLE), antiretroviral therapy adherence, virologic failure

INTRODUCTION

The 2017 HIV statistics revealed that globally, an estimated 36.9 million people were living with HIV, including an estimated 1.8 million new infections; with no reduction in these new infections from the previous year. More people living with HIV are accessing treatment and on average 80% of them were virally suppressed (1).

In 2014, the World Health Organisation (WHO) set the "90-90-90" target in an attempt to incite further action to achieve the interim 2020 goal which is aligned with the ambitious aim of ending the AIDS epidemic by 2030 (2). "The targets were that: 90% of all people living with HIV will know their HIV status; 90% of all people diagnosed with HIV infection will receive sustained antiretroviral therapy; and 90% of all people receiving antiretroviral therapy will achieve viral suppression" (3).

The highest concentration of people living with HIV (PLWH) is in low-and-middle income countries (LMIC) with an estimated 53% of the world's HIV-positive population located in Eastern and Southern Africa (4). South Africa, a Southern African LMIC, reported 13.1% of the general population to be HIV-infected (5). An estimated 7.52 million people living with HIV in South Africa know their status, 61% of these people are receiving ART, but only 47% are virally suppressed: slow progress towards the achievement of the "90-90-90" target (5, 6).

The expansion of access of ART for all people diagnosed with HIV has significantly reduced the mortality and morbidity rates of PLWH (2). According to the Joint United Nations Programme on HIV/ AIDS (UNAIDS) 2017 global data, 79% of people who knew their HIV status were accessing treatment of which approximately 80% were virally suppressed globally (1).

Benefits of better physical health and increased life expectancy are largely dependent on effective viral suppression. Suppression depends on people remaining in care and being adherent to their ART. Currently, there is no official standard measure of adherence to predict successful viral

suppression; it is generally accepted that a high level of adherence to ART is required (7, 8). Author, Schaecher (2013) articulated that, "Different classes of antiretroviral therapy (ART) are associated with different thresholds of adherence needed to achieve viral suppression and avoid resistance mutations" (p. 231). The challenge of life-long ART is sustaining this high level of adherence (9).

The converse is also true: previous research has demonstrated that non-adherence to ART is a strong predictor of virologic failure (10) (2, 11). Virologic failure has life-threatening consequences such as opportunistic infections, disease progression, drug resistance and death, as well as risk of transmission of HIV to sexual partners and unborn children (7, 12, 13).

In South Africa, the majority of PLWH live in disadvantaged communities and frequently experience HIV-and ART-related related challenges such as stigmatisation and discrimination which may be compounded by the experience of stressful life events such as interpersonal violence, psychological disorders, injuries, serious illness, housing instability, high levels of crime, difficulties in relationships, finances and employment; and death (14-16). These challenges are typical barriers to ART adherence and are associated with missed pills and follow-up appointments (14, 16, 17).

To improve our understanding of adherence behaviours, we examined the association between stressful life events and ART adherence in an ARV-naïve group over a 48-week period using electronic adherence monitoring as an objective adherence measure. In this secondary analysis, we hypothesized that the experience of stressful life events by PLWH will adversely impact their adherence to antiretroviral treatment and therefore affect virologic suppression. Covariates included in the analyses: age, gender, depression, anxiety and alcohol use are based on previous research which examined psychosocial and socio-demographic factors and found these factors to be significant predictors of nonadherence and virologic failure, particularly amongst PLWH in LMICs (7, 18-20). A recent Nigerian study reported a strong association between depression and negative life events; with women experiencing more negative life events than men (21).

METHODS

Study design, setting and population

A secondary analysis was conducted using retrospective data collected from a randomised control trial (RCT), previously approved by University of Cape Town Human Research Ethics Committee (UCT HREC reference 158/2012), which investigated the impact of a real-time electronic adherence monitoring device (EAMD) - Wisepill® -on antiretroviral treatment (ART) adherence in ART-naïve individuals over a 48- week period from 2012 to 2014 (22).

Parent study

230 HIV-infected individuals, both male and female, participated in the parent study. They attended the Hannan Crusaid Treatment Centre (HCTC), a large community-based ART clinic in Gugulethu, Cape Town – a peri-urban area with high levels of poverty and unemployment (22).

The eligibility criteria for the RCT included (1) ART-naive individuals aged ≥15 years old who commenced ART at HCTC; (2) who owned mobile phones; and (3) were able to give written consent or assent for participants who were ≤18 years old. Participation was offered to all eligible participants who attended the clinic between July 2012 and March 2013 (22). Convenience sampling was used and eligible "participants were randomised 1:1 to control and intervention arms. (22).

Secondary analysis

200 participants completed the RLE questionnaire shortly after the end of the study (week 48) and were eligible for the secondary analysis.

Data sources and measures

Several data sources obtained from the parent study were used for this analysis. The methods of the parent study have been described elsewhere (22). Baseline (week 0) demographic details taken from the parent study included age, gender, weight, height, CD4 count and viral load. Week 48 viral load was also collected.

Psychosocial covariates measured in the parent study included the 14-question Hospital Anxiety and Depression Score (HADS); and the four question CAGE score to identify alcohol issues (22). Both the HADS and CAGE questionnaires were completed at the Week 48 visit. Depression and anxiety were considered present in those with a HADS score of ≥ 8 for depression and/or ≥ 8 for anxiety. A CAGE score ≥2 indicated significant alcohol use.

Stressful life events were assessed using a Recent Life Event (RLE) questionnaire administered shortly after the week 48 visit to investigate the life events perceived to impact poor ART adherence. The RLE questionnaire included 19 questions on life events in eight categories such health, death, relationships, work, crime, birth, housing and other life events not mentioned in other categories. This was analysed as a continuous variable of frequency (count) of life events.

Cumulative ART adherence was measured using an electronic adherence monitoring device (EAMD, Wisepill®) and "calculated by the number of days the container was opened over the number of days in the period in care…" (22). For categorical analysis, taking ≥80% of the expected number of pills was considered to be adherent; and people were considered to have virologic failure with a week 48 HIV RNA ≥ 50 copies/ millilitre.

Statistical analysis

Data were cleaned and analysed using the STATA statistical package version 13.0 (STATA Corporation, College Station, TX).

Descriptive statistics were used to summarise the baseline demographics, adherence, VL measures and psychosocial measures: mean with standard deviations or median with interquartile ranges (IQR) for continuous data; and percentages for categorical data and to tabulate the frequency of life events data. The Chi-square test of independence was used to compare proportions.

Multivariate logistic regression analysis with preselected covariates were used to explore associations between life events and ART adherence, and between life events and virologic failure.

Individual SLEs were initially assessed in separate bivariate models to determine associations with ART adherence and VL; and SLEs with significant associations were included in the multivariate logistic regression models. Confounders of interest included age, gender, depression, anxiety and alcohol abuse, commonly found to influence adherence and VL, were assessed in these models.

Ethical approval

Ethics approval was obtained from the University of Cape Town Faculty of Health Science Research Ethics Committee, HREC reference 633/ 2019. All participants provided written informed consent in the parent study.

RESULTS

200 participants reached week 48 in the parent study (30 were lost to follow-up) and completed the Recent Life Event (RLE) questionnaire at the end of study; they comprised the cohort for this sub-

study with a median age of 32.7 years (IQR 27.4-41.7) and a predominance of females (67.5%). Most participants were in age groups 25-34 years (46.5%) and 35-44 years (28.5%).

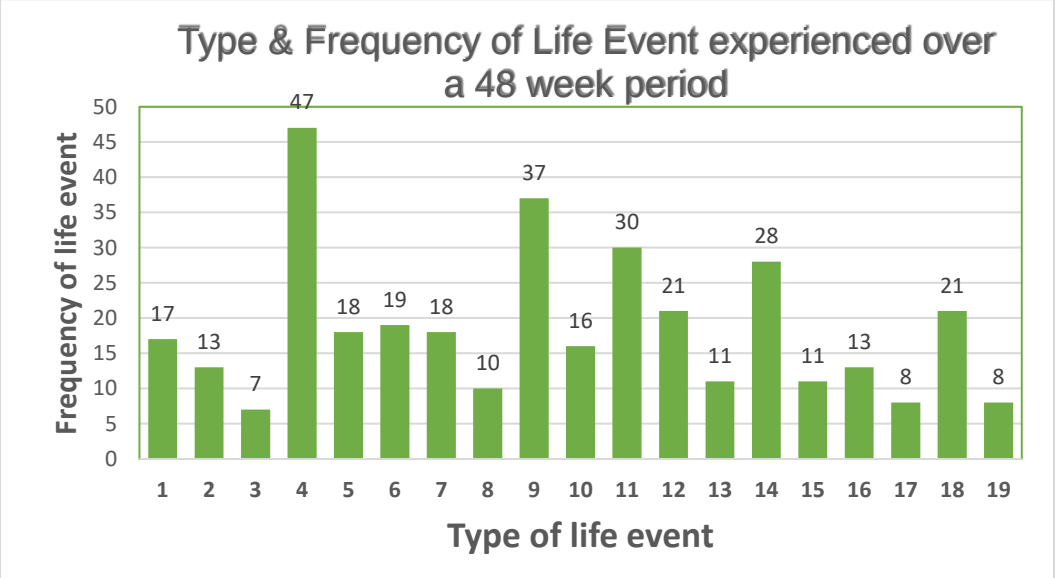
Table I. Baseline demographics and psychosocial characteristics of parent and sub-study cohorts

	Parent cohort	Sub-study cohort	n = 200	
			With VL at week 48	Without VL at week 48
N	230	200	182	18
Female sex: n (%)	150 (65.2)	135 (67.5)	123 (67.6)	12 (66.67)
Age in years: median (IQR)	32.8 (27.4-39.8)	32.7 (27.4-41.1)	32.9 (27.5-41.7)	28.6 (26.8-34.1)
Height (cm): mean (sd)	164.0 (8.6)	163.9 (8.2)	163.9 (8.1)	163.8 (9.0)
Weight (kg): median (IQR)	67.3 (57.8-79.6)	68.1 (58.2-80.4)	68.2 (58.9-80.2)	63.1 (53.3-81.7)
CD4 count: median (IQR)	225 (133-287)	232.5 (143.5-287.5)	233 (145–287)	210 (129-308)
Log HIV RNA (copies/ml): median (IQR)	4.9 (4.4-5.4)	4.8 (4.4-5.4)	4.9 (4.8-5.4)	4.8 (4.5-5.4)
HADS depression score of 8 or above: *n* (%)	74 (32.1)	63 (31.5)	59 (32.4)	4 (22.2)
HADS anxiety score of 8 or above: *n*(%)	89 (38.7)	76 (38)	70 (38.5)	6 (33.3)
CAGE ≥2: *n*(%)	35 (15.2)	30 (15)	25 (13.7)	5 (27.8)

At week 48, the median adherence in the sub-study cohort (n=200), was 82% (IQR 53-94%), indicating the cohort took medication 82% of the time according to the Wisepill® count. At week 48, 108 (54%) participants achieved an adherence level of ≥80% and 92 (46%) were <80%. adherent. 162 (89%) achieved viral suppression (HIV RNA ≤50 copies per millilitre) and 20 (11%) had virologic failure. Eighteen participants missed HIV-RNA testing at week 48. Compared to participants who had a HIV-RNA result at week 48, these participants were younger (28.6 years, IQR 26.8-34.1),

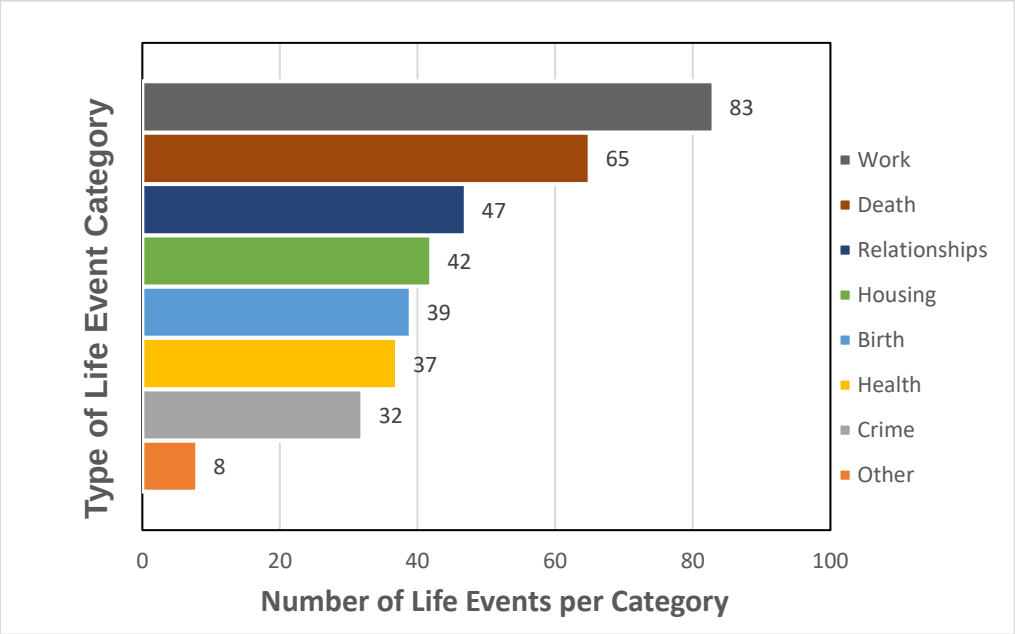
weighed less (63.1kg, IQR 53.3-81.7) and had more alcohol use (n=5, 27.8%), but neither difference reached significance.

Figure I. Type and Frequency of Life events



1-Personal - serious illness or injury, **2**-Immediate family - serious illness or injury, **3**-Other relatives or close friends - serious illness or injury, **4**-Death -Immediate family, **5**-Death -Other relatives or close friends, **6**-Separated from partner, **7**-Serious problem with a close friend, neighbour or relative, **8**-You or immediate family been abused, **9**-You or your partner been unemployed, **10**-Fired or retrenched?, **11**-Difficulty with debt, **12**-You or your immediate family been burgled or mugged, **13**-You been arrested by the police or been taken to court, **14**-You or someone at home given birth, **15**-Miscarriage / termination of pregnancy or still birth, **16**-Moved house (your own decision), **17**-Forced to move house, **18**-Housing difficulties, **19**-Other

Figure II. Number of Life events per category



A total number of 353 life events were recorded, with a median of 1.0 event per person (IQR 0-3).The most frequent individual events experienced were death in the immediate family (n=47, 13.31%), unemployment (n=37, 10.48%), financial problems (n=30, 8.5%) and birth (n=28, 7.93%). The event categories most frequently experienced were work, including unemployment and debt problems (n=83, 23.5%); death (n=65, 18.4%); relationship problems, including separation and abuse (n=47, 13.3%); housing problems (n=42, 11.9%) and birth events including favourable and poor birth outcomes (n=39, 11.1%).

Crude relationships between variables likely to impact on adherence and viral load were explored using the chi-square tests (Table II). These showed individuals with depression were more likely to have poor adherence (n=14, 56%), however this association was not statistically significant (X^2= 2.36, df=1, p=0.125). No other significant differences were observed between the other covariates and adherence (Table II) in this Chi-squared analysis.

For virologic failure, the only statistically significant difference was noted between the age groups of younger and older than 30 years (X^2=7.43, df=1, p=006), with younger people more likely to experience failure (Table II) . More females (n=14), fewer cases of depression (n=2, 8.0%) and anxiety (n=3, 8.1%); and no cases of alcohol use (n=0) were observed in people experiencing failure, but none met significance.

Table II. Chi-square test

Table II Chi-square test: Association between adherence or virologic suppression and covariates (alcohol abuse, anxiety, depression)

Variable	Case	Poor-adherence *n* (%)	Adherence *n* (%)	*n*	X^2 -statistic *(df)*	*P*-value
Gender						
Females		60 (44.4)	75 (55.6)	135	0.4046 (1)	0.525
Males		32 (49.2)	33 (50.8)	65		
Age						
Age <30 years		32 (45.7)	38 (54.3)	70	0.0035 (1)	0.953
Age >30 years		60 (46.2)	70 (53.4)	130		
Alcohol use	*Yes*	10 (45.5)	12 (54.5)	22	0.1415 (1)	0.707
	No	61 (41.2)	87 (58.8)	148		
Anxiety	*Yes*	15 (40.5)	22 (59.5)	37	0.0421 (1)	0.837
	No	56 (42.4)	76 (57.6)	132		
Depression	*Yes*	14 (56)	11 (44)	25	2.3565 (1)	0.125
	No	57 (39.6)	87 (60.4)	144		
Variable		**Virologic failure *n* (%)**	**Virologic suppression *n* (%)**	***n***	**X^2 -statistic *(df)***	***P*-value**
Gender						
Females		14 (11.4)	109 (88.6)	123	0.0599 (1)	0.807
Males		6 (10.2)	53 (89.8)	59		
Age						
Age <30 years		12 (20)	48 (80)	60	7.4303	0.006
Age >30 years		8 (6.6)	114 (93.4)	122		

Alcohol use	*Yes*	0 (0)	22 (100)	22	2.2845 (1)	0.131
	No	14 (9.5	133 (90.5)	147		
Anxiety	*Yes*	3 (8.1)	34 (91.9)	37	0.0032 (1)	0.955
	No	11 (8.4)	120 (91.6)	131		
Depression	*Yes*	2 (8.0)	23 (92.0)	25	0.0043 (1)	0.948
	No	12 (8.4)	131 (91.6)	143		

The total number of life events was significantly associated with virologic failure (OR 1.3, CI 1.06-1.6, p=0.011) but not with adherence (OR 1.09, CI 0.94-1.26; p=0.25) in univariate analysis. One individual life event, poor birth outcomes, was significantly associated with both poor adherence (OR 5.7, CI 1.2-27.31, p=0.028) and virologic failure (OR 6.5, CI 1.66-25.47, p=0.007). Regression analyses for all other individual life events were not significant; these data are not included here (available on request).

The multivariate regression models for both adherence and viral suppression included potential confounding / moderating covariates such as: age, gender, alcohol use, anxiety and depression. The results showed that the total number of events experienced had no significant association with poor adherence (aOR 1.13, CI 0.95-1.36, p=0.172) but came close to reaching significance for virologic failure (aOR 1.3, CI 0.97-1.75, p=0.077). Poor birth outcomes showed significant associations both with poor adherence (aOR 6.45, CI 1.25-33.29, p=0.026) and virologic failure (aOR 8.88, CI 1.55-50.58, p=0.014).

Further results from the multivariate analyses (table III & IV), show that age is a protective factor for virologic failure. The odds of failure decreased significantly with every year of increase in age (aOR 0.92, CI 0.85-0.99; p=0.048). Depression had a marginally significant association with poor adherence when a poor birth outcome is experienced (aOR 2.58, CI 1.01-6.58, p=0.047).

Table III. The impact of the total number events on adherence or viral load

Table III. below presents odds ratios (OR) or adjusted odds ratios (aOR) with 95% confidence intervals (CI) for the impact of the total number events on adherence or viral load

	Univariate model		Multivariate model	
Poor adherence (<80%) at week 48	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Total number of events	1.09 (0.94-1.26)	0.251	1.13 (0.95-1.36)	0.172
Age	0.99 (0.96-1.02)	0.576	0.98 (0.95-1.02)	0.421
Gender	1.21 (0.67-2.19)	0.525	1.5 (0.75-3.14)	0.237
Alcohol use	1.19 (0.48-2.93)	0.707	0.94 (0.36-2.50)	0.905
Anxiety	0.93 (0.44-1.94)	0.837	0.64 (0.28-1.50)	0.306
Depression	1.94 (0.82-4.5)	0.129	2.44 (0.97-6.13)	0.058
Virologic failure (HIV RNA >50 copies/ ml) at week 48 *				
Total number of events	1.3 (1.06-1.60)	0.011	1.30 (0.97-1.75)	0.077
Age	0.91 (0.85-0.97)	0.007	0.92 (0.85-0.99)	0.042
Gender	0.88 (0.32-2.42)	0.807	2.01 (0.58-6.96)	0.267
Anxiety	0.96 (0.25-3.64)	0.955	0.56 (0.11-2.81)	0.483
Depression	0.95 (0.2-4.52)	0.948	1.36 (0.24-7.81)	0.725

***Alcohol use was omitted – no cases of alcohol use with virologic failure were present**

Table IV. The impact of the individual event, poor birth outcomes, with adherence or viral load

Table IV. below presents odds ratios (OR) or adjusted odds ratios (aOR) with 95% confidence intervals (CI) for the impact of the individual event, poor birth outcomes, with adherence or viral load

	Univariate model		Multivariate model	
Poor adherence (<80%) at week 48	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Poor birth outcome	5.7 (1.2-27.31)	0.028	6.45 (1.25-33.29)	0.026
Age	0.99 (0.96-1.02)	0.576	0.98 (0.95-1.02)	0.435
Gender	1.21 (0.67-2.19)	0.525	1.6 (0.78-3.29)	0.194
Alcohol use	1.19 (0.48-2.93)	0.707	1.03 (0.39-2.74)	0.956
Anxiety	0.93 (0.44-1.94)	0.837	0.64 (0.27-1.49)	0.302
Depression	1.94 (0.82-4.5)	0.129	2.58 (1.01-6.58)	0.047
Virologic failure (HIV RNA>50 copies/ ml) at week 48 *				
Poor birth outcome	6.5 (1.66-25.47)	0.007	8.88 (1.56-50.58)	0.014
Age	0.91 (0.85-0.97)	0.007	0.92 (0.85-0.99)	0.048
Gender	0.88 (0.32-2.42)	0.807	2.89 (0.76-10.91)	0.118
Anxiety	0.96 (0.25-3.64)	0.955	0.56 (0.11-2.82)	0.482
Depression	0.95 (0.2-4.52)	0.948	1.29 (0.22-7.57)	0.781

***Alcohol use was omitted – no cases of alcohol use with virologic failure were present**

DISCUSSION

In our cohort of HIV-infected individuals in South Africa, who initiated ART and were followed over a 48-week period, stressful life events, particularly death of a family member, unemployment, debt, birth and being a victim of crime were common. We found the experience of a higher number of life events was associated with a higher risk of virologic failure. In our predominantly female cohort, individuals who experienced an adverse birth outcome were at higher risk of both poor adherence and virologic failure. Individuals with depression emerged at increased risk of poor adherence when a poor birth outcome was experienced, and younger individuals were at increased risk of virologic failure when a higher number of life events or an adverse birth outcome was experienced. In

contrast to other research, no associations were found between gender, depression, alcohol use and anxiety with ART adherence or virologic failure in our study.

Our findings are consistent with other research which used a similar stressful life event (SLE) measurement and found that participants who experienced a higher number of SLEs were less likely to achieve optimal ART adherence, with increased odds of virologic failure (14, 23, 24). Our findings add to the limited research in Africa on the impact of the number of SLEs on ART adherence and virologic failure (25). A previous study demonstrated this association using a monthly measurement of SLEs and pill count-based adherence (14). In our study, SLEs were measured using a long recall over a 48-week period and electronic adherence monitoring to provide a detailed, objective measurement. This is an important finding as the high burden of SLEs in a challenging resource poor context has the potential to reduce the likelihood to adherence significantly and consequently, increase potential drug resistance and virologic failure (14, 16). Our study findings did not show a significant association between the total number of events and poor adherence that would further explain the link to virologic failure.

Adverse birth outcomes such as miscarriage, abortion and stillbirth have been previously linked to postpartum depression and anxiety with long-term psychological impact for some women (26, 27). Importantly, depression and anxiety have been widely demonstrated in the literature to be associated with higher risk of poor ART adherence and virologic failure. (28, 29). Data from two recent South African studies, showed that pregnant women had lower adherence and more treatment interruptions; and the other study revealed that after ART initiation in pregnancy, 41% of postpartum women were not retained in care at 12 and 24- month follow up (30, 31). Together, these findings emphasise the vulnerability of pregnant and postpartum women and the increasing need for interventions and support during routine care as well as targeted retention strategies

Strengths of this study include the objective electronic adherence monitoring, the availability of psychosocial metrics included in multivariable models and high retention of this cohort

(approximately 87%). Limitations include: the missing data at week 48, resulting from missed visits in the parent study, which could have biased our study. This missing data could be associated with higher depression, anxiety, alcohol use and virologic failure, thus the analysis could have either have underestimated or overestimated the actual association of SLEs with the psychosocial covariates, poor adherence and virologic failure. Poor birth outcome data includes both individual and household responses and may not reflect an association between the individual's experience and poor adherence or virologic failure. The long recall period for the measurement of SLEs could be considered as another limitation of this study. Poor recall could potentially have omitted some SLEs resulting in an underestimation of the number of SLEs and the frequency of individual life events. In addition, the duration of individual life events was not analysed and therefore, the cumulative effect of life events on adherence could not be determined. The data could be further explored in future research to explain the relationship between the duration and cumulative effect of life events; and the mediating effect of covariates on the association between SLEs and adherence and virologic outcomes.

Despite these limitations, this study provides evidence on the important implications of common SLEs on ART adherence and viral load among PLWH< highlighting the need to develop targeted interventions to alleviate and mitigate the psychological impact of SLEs. Regular monitoring of SLEs and adherence has the potential to reduce the impact of SLEs and may improve the maintenance of good adherence. Although, some SLEs are unavoidable, the impact could possibly be reduced through effective support resources of social workers or social welfare networks and interventions to teach or improve coping skills.

CONCLUSION

SLEs are common in PLWH. This study concludes that the number of SLEs experienced negatively impact viral suppression and thus, requires particular attention and awareness during clinical care. These data highlighted the need for more supportive strategies and differentiated care models for younger PLWH, pregnant and postpartum women to improve lifelong engagement in HIV care which is vitally important in optimizing overall health outcomes for PLWH.

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PART D: APPENDICES

Appendix 1: Recent Life Event (RLE) Questionnaire

Date of visit	dd - mmm - yyyy	Patient number:	ZZ 9999

	Please tick the EVENT OCURRED box if the event happened to you. Please note the month the event occurred Please tick the EVENT STILL AFFECTS YOU box if the event is still having an effect in your life.	**Event ocurred:**	**Month of event e.g. Jan**	**Event still affects you**
HEALTH	1. Have you had a serious illness or been injured?			
	2. Has someone in your immediate family* had a serious illness or been injured?			
	3. Have any of your other relatives or close friends had a serious illness or been injured?			
DEATH	4. Has someone in your immediate family* died?			
	5. Have any of your other relatives or close friends died?			
RELATION-SHIPS	6. Have you separated from your partner (girl-or boy-friend, husband or wife)?			
	7. Have you had a serious problem with a close friend, neighbour or relative?			
	8. Have you, or an immediate family member been subject to any abuses (e.g. racial), attacks or threats?			
WORK	9. Have you or your partner been unemployed or seeking work for >1month?			
	10. Have you been fired or retrenched?			
	11. Have you had difficulty paying your bills or paying off your debts?			
CRIME	12. Have you or your immediate family been burgled or mugged?			
	13. Have you been arrested by the police or been taken to court?			
BIRTH	14. Have you or someone at home given birth?			
	15. Have you or someone at home had a miscarriage / termination of pregnancy or still birth?			
HOUSING	16. Have you moved house (your own decision)?			
	17. Have you moved house (not your own choice)?			
	18. Have you had any housing difficulties?			
OTHER	19. Have you experienced any other significant event? Please specify: _____			

* Immediate family includes: mother, father, partner, sister, brother, children

Completed by:	Staff sign and date	Checked by:	Staff sign and date

Appendix 2: Hospital Anxiety and Depression Score (HADS) Questionnaire

Hospital Anxiety and Depression Scale: Scoring Sheet

	Yes, definitely	Yes, some-times	No, not much	No, not at all
1. I wake early and then sleep badly for the rest of the night.	3	2	1	0
2. I get very frightened or have panic feelings for apparently no reason at all.	3	2	1	0
3. I feel miserable and sad.	3	2	1	0
4. I feel anxious when I go out of the house on my own.	3	2	1	0
5. I have lost interest in things.	3	2	1	0
6. I get palpitations, or sensations of 'butterflies' in my stomach or chest.	3	2	1	0
7. I have a good appetite.	0	1	2	3
8. I feel scared or frightened.	3	2	1	0
9. I feel life is not worth living.	3	2	1	0
10. I still enjoy the things I used to.	0	1	2	3
11. I am restless and can't keep still.	3	2	1	0
12. I am more irritable than usual.	3	2	1	0
13. I feel as if I have slowed down.	3	2	1	0
14. Worrying thoughts constantly go through my mind.	3	2	1	0

Add the scores for anxiety and depression:

- Anxiety 2, 4, 6, 8, 11, 12, 14: Total _____
- Depression 1, 3, 5, 7, 9, 10, 13 Total _____

GRADING: 0 - 7 = Non-case 8 – 10 = Borderline case 11+ = Case

Appendix 3: CAGE Questionnaire

Date:	dd - mmm - yyyy	Patient number:	ZZ 9999

CAGE questionnaire.

Ask the following questions:

1. Have you ever felt you needed to **C**ut down on your drinking? Yes □ No □
2. Have people **A**nnoyed you by criticizing your drinking? Yes □ No □
3. Have you ever felt **G**uilty about drinking? Yes □ No □
4. Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover? Yes □ No □

Each YES = 1 point. Write SCORE (1-4) here and on questionnaire CRF: **SCORE: _____**

[Two "yes" responses indicate that the possibility of alcoholism should be investigated further → place copy of this from in Hannan folder.]

Appendix 4: University of Cape Town HREC approval: Recent Life Event Questionnaire

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Amendment Form

Date	18 July 2012
HREC REF Number	**Your reference 158/2012**
Protocol number (if applicable) & Protocol title	**A randomised controlled Trial to explore Adherence-failure relationships in a South African antiretroviral delivery site using an electronic adherence device and sparse Pharmacokinetic sampling.**
Principal Investigator	Catherine Orrell
Department / Office Internal Mail Address	Desmond Tutu HIV Foundation, UCT Medical School, Anzio Road, Observatory, Cape Town 7925 South Africa.

List of Proposed Amendments with Revised Version Numbers and Dates

1. Recent Life Events Questionnaire -26Jun13 (Version 1)

HREC office use only (FWA00001637; IRB00001938)		
☑ Approved	☑ Type of review: Expedited	☐ Full committee
This serves as notification that all changes and documentation described above are approved.		
Signature Chairperson of the HREC	Signature Removed	Date: 04/07/2013

Appendix 5: University of Cape Town HREC approval letter

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shakirah.moonsamy@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 September 2019

HREC REF NO: 633/2019

Associate Professor Catherine Orrell
Desmond Tutu HIV Centre
UCT Faculty of Health Sciences
Observatory
Cape Town, 7925

Dear Associate Professor Catherine Orrell

PROJECT TITLE: THE IMPACT OF STRESSFUL LIFE EVENTS ON ANTIRETROVIRAL TREATMENT ADHERENCE AND VIRAL LOAD (SUB-STUDY LINKED TO 158/2012) (MASTER'S DEGREE-MS JA COOMBS)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

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 September 2020.

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)

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.

The HREC acknowledge that the student, *Ms J A Coombs* will also be involved in this study.

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

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB0000193B

Appendix 6: AIDS & Behavior Manuscript instructions

Journal home › Submission guidelines

AIDS and Behavior

Submission guidelines

Instructions for Authors

Manuscript Preparation

- Type double-spaced on one side of 8 ½ × 11-inch white paper using generous margins on all sides, (including copies of all illustrations and tables).
- A title page is to be provided and should include the title of the article, authors name (no degrees), authors affiliation, and suggested running head. The affiliation should comprise the department, institution (usually university or company), city, and state (or nation) and should be typed as a footnote to the authors name. The suggested running head should be less than 80 characters (including spaces) and should comprise the article title or an abbreviated version thereof. For office purposes, the title page should include the complete mailing address, telephone number, fax number, and email address of the one author designated to review proofs.
- With the exception of Brief Reports and Behavioral Surveillance Reports, initial submissions to AIDS and Behavior do not have word or page limits. Briefer and more succinct papers tend to review better and papers may be reduced in length as part of the review process. However, the length of the original submission is left to author discretion.
- An abstract is to be provided, preferably no longer than 150 words.

- A list of 4-5 key words is to be provided directly below the abstract. Key words should express the precise content of the manuscript, as they are used for indexing purposes.
- All sections should carry headings (such as INTRODUCTION, METHODS, RESULTS, DISCUSSION, CONCLUSIONS, etc.), typed flush left. All acknowledgments (including those for grant and financial support) should be typed in one paragraph (so−headed) on a separate page, that directly precedes the References section.
- Illustrations (photographs, drawings, diagrams, and charts) are to be numbered in one consecutive series of Arabic numerals. The captions for illustrations should be typed on a separate sheet of paper. All illustrations must be complete and final, i.e., camera-ready. Photographs should be large, glossy prints, showing high contrast. Drawings should be high quality laser prints or should be prepared with india ink. Either the original drawings or good−quality photographic prints are acceptable. Artwork for each figure should be provided on a separate sheet of paper. Identify figures on the back with authors name and number of the illustration. Electronic artwork submitted on disk should be in the TIFF or EPS format (1200 dpi for line and 300 dpi for halftones and grayscale art). Color art should be in the CYMK color space. Artwork should be on a separate disk from the text, and hard copy must accompany the disk.
- Tables should be numbered (with Roman numerals) and referred to by number in the text. Each table should be typed on a separate sheet of paper. Center the title above the table and type explanatory footnotes (indicated by superscript lowercase letters) below the table.
- AIDS and Behavior does not have a limit on number of authors. However, if deemed to be excessive the editor may request author justifications and reductions.

AIDS and Behavior uses Vancouver style as outlined in the American Medical Association Manual of style: A Guide for Authors and Editors, 10th Edition.

A reference number is allocated to a source in the order in which it is cited in the text. In text, identify references as Arabic numerals in brackets (1). If the source is referred to again, the same number is used. References are listed in numerical order in the Reference List at the end of the paper. Do not alphabetize. Use abbreviated names of journals according to the journal

list in PubMed. List all authors and/or editors up to 6; if more than 6, list the first 3 followed by “et al.” The following are examples.

1) McKirnan DJ, Vanable PA, Ostrow DG, Hope B. Expectancies of sexual "escape" and sexual risk among drug and alcohol-involved gay and bisexual men. J Subst Abuse. 2001;13(1-2):137-54.

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Verify that every instance of a number in text corresponds to the numbered reference.

Footnotes should be avoided. When their use is absolutely necessary, footnotes should be numbered consecutively using Arabic numerals and should be typed at the bottom of the page to which they refer. Place a line above the footnote, so that it is set off from the text. Use the appropriate superscript numeral for citation in the text.

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