



Prevalence of anxiety and depression in a predominantly HIV-infected population with severe cutaneous adverse drug reactions

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Declaration

I, Eddy M. Zitha, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
CADR	Cutaneous adverse drug reactions
CDC	Centre for Disease Control
CIDI	Composite international diagnostic inventory
DIHS	Drug-induced hypersensitivity syndrome
DLQI	Dermatology Life Quality Index
DM	Diabetes mellitus
DRESS	Drug reaction with eosinophilia and systemic symptoms
HADS	The hospital anxiety and depression scale
HAD-A \geq 8	The hospital anxiety and depression scale – positive anxiety score
HAD-D \geq 8	The hospital anxiety and depression scale – positive depression score
HHV	Human herpesvirus
HIV	Human immunodeficiency virus
HIV/AIDS	Human immunodeficiency virus infection / acquired immunodeficiency syndrome
HSV	Herpes simplex virus
IQR	Interquartile range
LMICs	Lower and middle income countries
Mixed A-D	Mixed anxiety and depression symptoms
NVP	Nevaripine
Rif	Rifampicin
PIH	Post inflammatory hyperpigmentation
SCADR	Severe cutaneous adverse drug reaction(s)
SCORTEN	SCORE of toxic epidermal necrolysis

SJS	Stevens-Johnson syndrome
SJS/TEN	Stevens-Johnson syndrome and toxic epidermal necrolysis
SJS-TEN	Stevens-Johnson syndrome and toxic epidermal necrolysis overlap
TEN	Toxic epidermal necrolysis
TB	Tuberculosis
WHO	World Health Organization

Table of Contents

Declaration	I
Acknowledgements	II
Conference outputs resulting from this thesis	III
Abbreviations	IV
List of Tables	VII
List of Figures	VII
Appendixes	VIII
PROTOCOL	1
Original protocol as approved by the Departmental Research Committee and Faculty Research Ethics Committee	2
Introduction	2
Method.....	4
Inclusion Criteria.....	5
Exclusion Criteria.....	5
Consent	5
Storage of data and information.....	6
Publication of data	6
Conflict of interest.....	6
Institutional Approval	6
Funding.....	7
Amendments to Original Protocol	7
CHAPTER 1: LITERATURE REVIEW	8
1. BACKGROUND and LITERATURE REVIEW	9
1.1. Search strategy and selection criteria	9
1.2. SJS/TEN	9
1.2.1. SJS/TEN definition.....	9
1.2.2. SJS/TEN Epidemiology	10
1.2.3. SJS/TEN pathogenesis.....	11
1.2.4. SJS/TEN clinical features	12
1.2.5. Acute complications.....	15
1.2.6. Long-term chronic complications	15
1.2.7. Management of SJS/TEN	22
1.2.8. Prognosis.....	23
1.3. DRESS	24
1.3.1. Definition of DRESS	24
1.3.2. DRESS epidemiology	25

1.3.3. DRESS pathogenesis	25
1.3.4. DRESS clinical features	27
1.3.5. Long-term complications	29
1.3.6. Management	30
1.3.7. Prognosis	31
1.4. Anxiety and depression in the general population of Lower and Middle Income Countries (LMICs).....	31
1.5. Anxiety and depression in HIV-infected patients in LMICs	32
1.6. Anxiety and depression in HIV-positive versus HIV-negative population	33
1.7. Anxiety and depression in hospitalized patients	34
1.8. Anxiety and depression in Adverse Drug Reactions	34
1.9. Anxiety and depression in SJS/TEN sequelae	35
1.10. Anxiety and depression in DRESS sequelae	35
1.11. Instruments available to assess depression and anxiety	35
CHAPTER 2: STUDY AIMS AND OBJECTIVES	39
2.1 STUDY AIMS and OBJECTIVES.....	40
Hypothesis.....	40
Aim	40
2.2. MATERIALS and METHODS.....	41
2.2.1. Study population and recruitment	41
2.2.2. Instruments	42
2.2.3. Data collection	44
2.2.4. Statistical analysis and data presentation	45
2.2.5. Source of funding.....	46
2.2.6. Ethics.....	46
CHAPTER 3: STUDY RESULTS.....	47
3.1. RESULTS	48
3.1.1. Participants at six weeks.....	48
3.1.2. SCADR patients with cases of anxiety at six weeks	52
3.1.3. SCADR patients with cases of depression at six weeks	53
3.1.4. SCADR patients with cases of comorbid anxiety and depression at six weeks	54
3.1.5. SCADR patients and quality of life at six weeks	55
3.1.6. Participants at six months.....	56
3.1.7. SCADR patients with cases of anxiety at six months.....	57
3.1.8. SCADR patients with cases of depression at six months	58
3.1.9. SCADR patients with cases of comorbid anxiety and depression at six months.....	59
3.1.10. SCADR patients and quality of life at six months.....	60
3.1.11. SCADR patients with suicidal ideation at six weeks	61
CHAPTER 4: DISCUSSION	64
4.1. DISCUSSION.....	65
CHAPTER 5: RECOMMENDATIONS	74

5.1. RECOMMENDATIONS.....	75
5.2. ACKNOWLEDGEMENTS.....	75
5.3. SOURCES OF FUNDING:.....	76
REFERENCE:.....	97

List of Tables

Table 1. Demographics of cases at six weeks and six months.....	49 - 50
Table 2. Anxiety classification of SCADR patients at six weeks and six months follow-up using the HADS score for anxiety ^a	62
Table 3. Depression classification of SCADR patients at six weeks and six months follow-up using the HADS score for depression ^a	62
Table 4. Caseness classification of SCADR patients at six weeks and six months follow-up using the HADS score for caseness ^a	63
Table 5. Quality of life classification of SCADR patients at six weeks and six months follow-up using the DLQI score ^a	63

List of Figures

Figure 1. Stevens-Johnson syndrome: Haemorrhagic cheilitis.....	14
Figure 2. Stevens-Johnson syndrome: Extensive skin necrosis, early stripping and mucositis.....	14
Figure 3. Toxic epidermal necrolysis: Extensive epidermal necrosis and stripping .	15
Figure 4. Post-inflammatory hyperpigmentation in a patient with resolved Stevens-Johnson syndrome	17
Figure 5. Microstomia in a patient who had severe haemorrhagic cheilitis in associated with Stevens-Johnson syndrome.....	18
Figure 6. Severe Beau’s lines with pterygium of the nails in a patient with resolved Stevens-Johnson syndrome.	19
Figure 7. Introital stenosis in a patient with resolved Stevens-Johnson syndrome..	21

Figure 8. Discolouration of teeth post Stevens Johnson syndrome	22
Figure 9. A drug reaction with eosinophilia and systemic symptoms: scale, facial oedema, erythema and cheilitis	28
Figure 10. Flow chart of eligible recruited and lost to follow-up of patients.....	49

Appendixes

Appendix 1: Ethical approval: Assessment of the short term and medium term psychological impact	78
Appendix 2: Annual progress report form	79
Appendix 3: Prospective cohort study Consent in English.....	80 - 81
Appendix 4: Prospective cohort study Consent in Afrikaans.....	82 - 83
Appendix 5: Prospective cohort study Consent in Isixhosa	84 - 85
Appendix 6: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in English.....	86
Appendix 7: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in Afrikaans.....	87
Appendix 8: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in Isixhosa	88
Appendix 9: Data collection Dermatology Life Quality Index (DLQI) in English	89
Appendix 10: Data collection Dermatology Life Quality Index (DLQI) in Afrikaans .	90
Appendix 11: Data collection Dermatology Life Quality Index (DLQI) in Isixhosa ...	91
Appendix 12: The raw data for each patient.....	92- 96

ABSTRACT

Background: There is limited data on anxiety and depression in subjects with severe cutaneous adverse drug reactions (SCADR), in a predominantly HIV-infected population. The aim of the study was to prospectively investigate the prevalence of anxiety and depression and quality of life in patients with SCADR.

Methods: In this prospective study, SJS, SJS-TEN, TEN and DRESS patients were assessed for anxiety and depression using validated scoring systems, the Hospital Anxiety and Depression Scale (HADS), and the Dermatology Life Quality Index (DLQI). This was done at six weeks post discharge and again at six months follow-up.

Results: Forty-eight patients with SCADR were enrolled at six weeks and 37/48 (77%) completed the study at six months. The populations were similar demographically at six weeks and six months.

At six weeks anxiety or borderline anxiety symptoms/caseness was identified in 25/48 (52%) SCADR patients and depression or borderline depression symptoms/caseness in 24/48 (50%). However, of those with symptoms, 18 were assessed as having co-morbid anxiety and depression with only 2 cases of pure anxiety and 4 of pure depression. At six months only 37 patients with SCADR returned for follow-up. Four of them had died in the interim while the other seven relocated. Of the cases of pure anxiety; one resolved and one was lost to follow-up. Of the cases of pure depression; one resolved, one persisted, one converted to comorbid anxiety and depression and one was lost to follow-up. Of those with co-morbid anxiety and depression 10 persisted, 2 converted to pure depression, 3 normalised and 2 were lost to follow-up. One previously normal patient developed

anxiety symptoms and one case developed comorbid anxiety and depression.

In 9/13 (69%) of the patients with SJS, SJS-TEN and TEN, co-morbid anxiety and depression persisted from week six to 6 months. In contrast in only 1/5 (20%) of the patients with DRESS, co-morbid anxiety and depression persisted from week six to 6 months. The cases of pure anxiety and depression were too small for meaningful comment.

The overall SJS, SJS-TEN and TEN had median DLQI 8.4 relative to DRESS (DLQI 7.5) at six weeks. However, TEN (DLQI 14) had a greater impact on the quality of life compared to SJS (DLQI 3) and DRESS (DLQI 7.5). This pattern was maintained at six months.

Conclusion: Anxiety and depression in patients with SCADR in a predominantly HIV-infected population is present. In the majority of cases, depression and anxiety coexist in patients with SCADR. These are sustained for at least 6 months post discharge. SCADR has a negative impact on quality of life. Our findings should help to improve the awareness of the impact of severe cutaneous adverse drug reactions on mental health especially as this may impact on future treatment adherence.

PROTOCOL

Original protocol as approved by the Departmental Research Committee and Faculty Research Ethics Committee

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Introduction

Cutaneous adverse drug reactions (CADR) are common and pose a major health problem for patients and drain significant resources. CADR is defined as any undesirable change in the structure or function of the skin, its appendages or mucous membranes as a result of drug use and it encompasses all adverse events related to drug eruption, regardless of the aetiology (Jelvehgari et al., 2009). The reactions can either be confined to the skin only or be part of a multisystem disorder. CADR has a wide variety of clinical presentations. These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug hypersensitivity syndrome (DHS) or drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruption (FDE), urticaria, morbiliform eruption, cutaneous vasculitis, lichenoid drug eruption, psoriasiform eruption and acute generalized exanthematous pustulosis (AGEP). An individual drug can cause multiple types of CADR and a specific type of CADR can be due to any drug. In many patients, CADR present as a

self-limiting complication with minor consequences. However, there may be considerable morbidity and mortality associated with some severe cases.

Unfortunately, there is no definition of severity in CADR that is in general use.

Severity is often based on the type of drug reaction and mortality associated with that specific type of CADR. SJS, TEN, DHS, cutaneous vasculitis and bullous fixed drug eruption are considered severe forms of CADR. Some authors define severity based on the need for hospitalization, interruption of therapy or change of therapy. These are clearly not ideal definitions. Common Terminology Criteria for Adverse Events (CTCAE) grading, which is a standardized classification of side effects used in assessing drugs for cancer therapy is used extensively in clinical drug trials. This, in our opinion is currently the best available standardized method of assessing severity of CADR that should be used in clinical trials involving the different types of CADR.

There is limited data on the short-term and medium-term sequelae following severe CADR, most of these being case reports. Long-term sequelae reported in the literature include blindness, post inflammatory hyperpigmentation, scarring, adenosis, lip adhesion, airway obstruction, vaginal stenosis, hematocolpos and heterotrophic ossification (Allanore, 2007, Gibson and Poduri, 1997, Marinho et al., 1999, Murphy and Brant, 1998, Niemeijer et al., 2009, Tsubota and Shimazaki, 1999). A few studies have shown that dermatologic toxicities have an impact on patients' physical, functional, emotional, and social well-being (Berrino et al., 2005, Wagner and Lacouture, 2007). However, there are a few studies that have systematically assessed psychological medium-term and long-term effects of severe CADR. The Hospital anxiety and depression scale (HADS) are a validated useful screening method (Bjelland et al., 2002, Zigmond and Snaith, 1983) in a form of a

questionnaire that performs well in screening for the separate dimensions of anxiety and depression in patients from non-psychiatric hospital clinics, a 14-item scale, which are rated on a scale of 0-3, indicating the strength of agreement with that item (Bjelland et al., 2002, Zigmond and Snaith, 1983). The Dermatology Life Quality index (DLQI), a validated self-administered questionnaire of 10 questions, each scored on a 4-point Likert scale (0-3), concerning the patients' perception of the impact of the skin diseases on different aspects of their quality of life, for dermatological patients over the age of 16 years (Finlay and Khan, 1994).

Method

When the Human Research Ethics Community approves the study, 50 patients over the age 18 admitted with the primary diagnosis CADR in the Dermatology, at Grootte Schuur Hospital will be recruited with 20 controls. These patients are routinely followed up at 6 weeks and at 6 months post-discharge as a standard of care. All patients will be given a written consent before participating in the study. A Validated questionnaires (HADS and DLQI), which measures symptoms of anxiety and depression will be administered by one of the co-investigators or a trained nurse and will take approximately 45 minutes to administer. The questionnaire will be in English, Afrikaans and Xhosa and a person competent in that language will administer each. The study will be carried for a period of six to twelve months, where, the same questionnaires will be administered at these visits.

Inclusion Criteria

- Participants above the age of 18 who are willing and able to give consent
- Participants diagnosed with CADR that warranted admission to hospital
- Participants who are willing and able to answer the questionnaires on two occasions 4 months apart

Exclusion Criteria

- Participants who are under the age of 18 of age without parents/guardian's consent
- Participants who are unable or unwilling to give informed consent
- Participants who are unwilling and able to come for follow-up on two occasions 4 months apart

Consent

Consent will be taken by one of the investigators. In cases where there is a language barrier a trained translator competent in the participant's mother tongue will be used. Consent forms will be provided in English, Xhosa and Afrikaans. Participants will be

informed of the outcomes of the study and if needed, appropriate referral for further management will be made.

Storage of data and information

All the physical data collected during the study will be kept confidential in a locked area and will only be available to authorized staff. Electronic data will also be stored in a password-restricted computer only accessible to authorized staff.

Publication of data

There are no restrictions on the publication of the outcomes of the study.

Conflict of interest

There is no funding that has been secured for the study and the authors have no conflict of interest in the outcomes of the study.

Institutional Approval

This proposal has been approved by the University of Cape Town Research Ethics Committee.

Funding

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Amendments to Original Protocol

Method - additional sample of 20 controls was added and change referencing from numerical superscripts to first author in parenthesis in the text

CHAPTER 1: LITERATURE REVIEW

1. BACKGROUND and LITERATURE REVIEW

1.1. Search strategy and selection criteria

Electronic databases were searched for relevant articles. We searched PubMed, Google Scholar, ScienceDirect and EBSCOHost using keywords in different combinations. Search terms included, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), a drug reaction with eosinophilia and systemic symptoms/ drug-induced hypersensitivity syndrome (DRESS/DIHS), incidence, prevalence, severe cutaneous adverse drug reaction (SCADR), human immunodeficiency virus (HIV), hospitalization, anxiety and depression. We also looked for studies that assessed anxiety and depression in HIV infected persons, as well as in hospitalised patients. There were 8 studies in total that assessed anxiety and depression in HIV (Berger-Greenstein et al., 2007, Marwick and Kaaya, 2010, Martinez et al., 2008, Olley et al., 2003, Freeman et al., 2007, Myer et al., 2008, Mayston et al., 2012, Hughes et al., 2004).

1.2. SJS/TEN

1.2.1. SJS/TEN definition

Stevens-Johnson syndrome (SJS) was first described in 1922 by two American paediatricians, Dr Albert Mason Stevens and Dr Frank Chambliss Johnson. It became known as SJS following their publication describing two young patients with

severe muco-cutaneous disease, who recovered 22 days after onset of illness (Stevens and Johnson, 1922). In 1956, Alan Lyell described four patients with an eruption resembling scalding of the skin which he called toxic epidermal necrolysis (TEN) (Lyell, 1956). Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are considered to be part of a spectrum of the same disease, differing only by the extent of skin detachment. In Stevens-Johnson syndrome, there is 10% of epidermal detachment and in TEN there is >30% detachment. SJS-TEN overlap lies between these two extremes with an epidermal detachment between 10 and 30% of the body surface area (Bastuji-Garin et al., 1993).

1.2.2. SJS/TEN Epidemiology

Stevens-Johnson syndrome and toxic epidermal necrolysis has a worldwide incidence of approximately 0.05 to 3 cases/million per year (Bastuji-Garin et al., 1993, Fritsch and Sidoroff, 2000). This may be as high as 1-2 cases per 1000 individuals with HIV-infected subjects (Mittmann et al., 2012). Sub-Saharan Africa has the highest prevalence of HIV, accounting for 68% of the global burden of the disease (Khambaty and Hsu, 2010, Mosam et al., 2004, Punyaratabandhu et al., 2012, Sidibé, 2011, Ukonu and Eze, 2012); making this area a high risk for SJS/TEN. Drugs that are used for the treatment of HIV and associated opportunistic infections have a strong association with SJS/TEN (CDC, 2013, Mittmann et al., 2012). Two tertiary referral centres in Cape Town, South Africa, have reported that up to 80% of SJS/TEN cases seen were in HIV infected persons. In a cohort of 298 patients admitted at Groote Schuur Hospital with CADR, 65 had TB associated CADR of which 92% were HIV infected. The majority of those (54%) with TB

associated CADR had SJS/TEN (Lehloenya et al., 2011). Similarly, 79% of patients with SJS/TEN seen at Tygerberg Hospital, were found to be HIV infected (Kannenbergh et al., 2012). Nevirapine (NVP) has been the most frequently implicated drug causing SJS/TEN in Africa and Europe with a fatality rate of 22.5% (Sidibé, 2011, Fagot et al., 2001). In comparison, in Europe and Western Asia, allopurinol is most frequently implicated medication causing SJS and TEN (Halevy et al., 2008). Numerous other drugs have been implicated as etiologic agents of SJS/TEN, including antiepileptics, non-steroidal anti-inflammatory drugs, antibacterial sulphonamides, other antiretroviral (ARV) drugs and anti-tuberculosis drugs (Auquier-Dunant et al., 2002, Mockenhaupt and Norgauer, 2002, Mockenhaupt et al., 2008, Rotunda et al., 2003).

1.2.3. SJS/TEN pathogenesis

The detailed pathogenesis of SJS/TEN is still not completely understood.

Immunological reactions, genetic predisposition and infections have been suggested to play a role.

1.2.3.1. Immunological mechanisms

Apoptosis of keratinocytes mediated by cell-autonomous Fas (CD95)/Fas-ligand interaction and/or cytotoxic T-cell release of perforin, granzyme B and granulysin seems to play a key role in the pathogenesis of SJS/TEN (Chung et al., 2008).

1.2.3.2. Genetic predisposition

A genetic predisposition to adverse drug reactions is increasingly described in the literature. Human leukocyte antigen (HLA) genes have been identified as predictors for SJS/TEN. This was first reported by Chung et al., who showed an association between the HLA-B*1502 allele, SJS/TEN and carbamazepine in 100% of Han Chinese SJS/TEN cases (Chung et al., 2004). Hung et al., also identified the HLA-B allele B* 5801 as a genetic marker for allopurinol-SJS/TEN in Han Chinese (Hung et al., 2005). A recent study found a TRAF3IP2 gene to be associated with nevirapine-induced SJS/TEN in 27 Mozambican patients (Ciccacci et al., 2015).

1.2.3.3. Infections

Reactivation of human herpesviruses (HHV) including herpes simplex, HHV 6, HHV 7, Epstein-Barr virus, and cytomegalovirus, against which the body mounts a strong immune response have been implicated in the pathogenesis (Ichiche et al., 2003, Picard et al., 2010). *Mycoplasma pneumoniae* has also been implicated in the pathogenesis of SJS/TEN without drug exposure, especially in children. Finkelstein et al., reported that 22% of children with SJS/TEN had acute *M. pneumoniae* infection and 9% had herpes simplex virus after observing 51 children with SJS/TEN in the Hospital for Sick Children and Children's Hospital in Boston (Finkelstein et al., 2011).

1.2.4. SJS/TEN clinical features

In the acute phase, initial symptoms can be non-specific. Patients may initially present with pain or a burning sensation of the skin and mucosal surfaces over a

period of 72 hours. This is often confused with an upper respiratory tract infection and treated as such (Chang et al., 2007, Martin and Li, 2008, Sotozono et al., 2009). The rash initially manifests as erythematous macules over the trunk and extremities. As the red areas enlarge, central dusky necrotic sites develop with subsequent bullae formation (Figure 1). The palms and soles are often involved, with tenderness, erythema, epidermal necrosis and blistering. Mucositis occurs in more than 90% of patients (Harr and French, 2010, Martin and Li, 2008). Haemorrhagic cheilitis is characteristic (Figure 1) but genital and ocular mucosal erosions are also common. Systemic features such as fever and malaise often accompany the rash. Involvement of internal organs is not a commonly described feature of SJS/TEN. SJS-TEN overlap lies between these two extremes (Figure 2). The disease manifests clinically as epidermal stripping and baring of large areas of the dermis and mucosal membranes, with resultant skin and mucosal failure. TEN is the most severe form (Figure 3) of the disease.



Figure 1. Stevens-Johnson syndrome: Haemorrhagic cheilitis



Figure 2. Stevens-Johnson syndrome: Extensive skin necrosis, early stripping and mucositis



Figure 3. Toxic epidermal necrolysis: Extensive epidermal necrosis and stripping

1.2.5. Acute complications

Extensive skin blistering and erosions lead to skin failure. This manifests as thermoregulatory disturbances, increased electrolyte imbalance, transdermal fluid loss and infections. Difficult, painful swallowing as a result of oropharynx erosions perpetuates the resultant fluid depletion. Tracheobronchial shedding with resultant respiratory failure may occur in the acute phase. Bacterial systemic infection can result from skin failure or gastrointestinal and genitourinary epithelial barrier loss. This is the most frequent cause of death in patients with SJS/TEN (Knight et al., 2014).

1.2.6. Long-term chronic complications

SJS/TEN is a debilitating disease with long-term sequelae of varying severity. These occur in 73% of patients who present with mucosal involvement in the acute phase. They range from moderate dry eye syndrome to blindness, oesophageal strictures with anal stenosis; nail dystrophies; hematocolpos, vulvovaginal synechiae, phimosis, urethral strictures; heterotrophic calcifications; dyspigmentation and hypertrophic scars (Magina et al., 2003, Oplatek et al., 2006, Sheridan et al., 2002, Yip et al., 2007). Microstomia and teeth abnormalities may also result. Some of these sequelae are shown in Figure 4 to Figure 8.

1.2.6.1. Dyspigmentation

A study conducted by Revuz and colleague in 1987 at Hôpital Henri Mondor in Créteil, France reported that among 87 patients with TEN, pigmentary changes were frequently observed sequelae from 65 patients who survived (Revuz et al., 1987). According to the study of Magina et al., 63% of patients with TEN were found to have hyper-and hypopigmentation of the skin (Figure 4) and this was reported as a common sequelae of late phase TEN (Magina et al., 2003).



Figure 4. Post-inflammatory hyperpigmentation in a patient with resolved Stevens-Johnson syndrome

1.2.6.2. Gastro-oesophageal

Powell et al., described a 17-year man with SJS secondary to phenytoin. In addition to his typical skin lesions he had ocular and oral mucosal lesions. He complained of severe gastrointestinal symptoms associated with a progressive, inflammatory pancolitis. Colonoscopy showed an erythematous, friable mucosa with ulceration and mucopurulent exudates throughout the colon (Powell et al., 2006).

Mashiko et al. described a 53-year old hospitalized female with TEN secondary to ibuprofen. The patient was admitted on presentation with fever and progressive partial thickness skin loss. Diagnostic biopsy confirmed TEN. She complained of no

pain, but difficulty in taking meals or undergoing dental therapy. Physical examination revealed bilateral fibrotic scar bands on the oral commissures, which narrowed the oral orifice and caused microstomia (Figure 5). They found scar bands located on and medial to the vermillion, where the maximal interlabial and intercommissural distances were measured 25 and 28 mm (Mashiko et al., 2013).



Figure 5. Microstomia in a patient who had severe haemorrhagic cheilitis in associated with Stevens-Johnson syndrome.

1.2.6.3. Nail dystrophies

In a study conducted by Magina et al., in Portugal in 2003, of eight patients with TEN who survived, 3 had nail dystrophies¹⁹⁸⁷ (Figure 6) (Magina et al., 2003).



Figure 6. Severe Beau's lines with pterygium of the nails in a patient with resolved Stevens-Johnson syndrome.

1.2.6.4. Ocular complications

The severity of corneal ulceration, synaechiae formation and scarring ranges from mild to severe and is often the result of poor eye care during the acute stages. In a study of 366 patients with SJS/TEN, 24% developed ocular complications (Power et al., 1995). Chronic sequelae occur in approximately 35% of patients (Power et al., 1995, Yetiv et al., 1980). Dry eyes are a major problem for survivors of SJS/TEN as it leads to blindness (De Rojas et al., 2007). Other delayed sight-threatening complications

are recurrent conjunctival inflammation (Foster et al., 1988), ocular mucous membrane pemphigoid (Chan et al., 1991) and late diffuse scleritis (De Rojas et al., 2007).

1.2.6.5. Vulvovaginal complications

In a study by Meneux et al., 70% of patients reported genital lesions during the acute phase of TEN. Among these, in 89% of the cases only the vulva was involved and in 11% erosions involved both the vulva and the vagina (Figure 7). Five patients had long-term sequelae; three had dyspareunia of which two required surgery. Surgery failed to relieve dyspareunia in one of them (Meneux et al., 1998). The prevalence of labial adhesion and introital stenosis as high as 18%, has been described in patients with SJS/TEN (Meneux et al., 1998, Niemeijer et al., 2009). Hematocolpos in a case of SJS was associated with amenorrhea and cyclical abdominal pain (Murphy and Brant, 1998).



Figure 7. Introital stenosis in a patient with resolved Stevens-Johnson syndrome.

1.2.6.6. Dental complications

Periodontal disease is a common consequence in acute phases of SJS/TEN (Figure 8). All 16 of their patients complained of oral discomfort, nine of the 16 patients had altered oral mucosa, 13/16 had gingival inflammation, 14/16 had gingival recession and 6 had gingival synaechiae (Gaultier et al., 2009). All the patients had sicca symptoms with abnormal salivary viscosity after the acute phase of SJS/TEN.



Figure 8. Discolouration of teeth post Stevens Johnson syndrome

1.2.6.7. Heterotopic ossification

Heterotopic ossification is described by Major et al., as a process resulting from an interaction of soft tissue oedema, vascular stasis, tissue hypoxia, aggregation of calcium, and osteoblasts with osteoplastic activity (Major et al. (1980). It has been reported as a complication of TEN (Gibson and Poduri, 1997).

1.2.7. Management of SJS/TEN

There is a general consensus that earlier withdrawal of the causative drug and referral to a tertiary centre with experience in managing SJS/TEN improves the prognosis (Garcia-Doval et al., 2000, Sheridan et al., 2002). It is controversial whether other treatment modalities such as systemic steroids, cyclosporine A,

intravenous immunoglobulins or prophylactic antibiotics are beneficial. Antibiotics should only be used in the presence of clinical and/or microbiological features of an infection. Supportive therapy, including good skin hygiene, wound care; temperature control, maintenance of fluid and electrolyte balance and infection control is the mainstay of therapy. Nutritional support with good nursing care should be started as soon as possible. These paired with a multidisciplinary approach improves survival and reduces infection and long-term sequelae (Lee et al., 2012, Magina et al., 2003, Mockenhaupt, 2011, Mockenhaupt and Roujeau, 2010, Sheridan et al., 2002, Yip et al., 2007).

1.2.8. Prognosis

The prognosis of individual patients can be evaluated by applying a severity of illness score, the TEN-specific severity-of-illness score (SCORTEN). This is calculated using parameters that include age, extent of skin detachment, underlying malignancy, heart rate and laboratory parameters (Bastuji-Garin et al., 2000). SCORTEN is a reliable instrument for prognostication, but was not designed to predict any long-term sequelae. It is a validated score most accurate when performed in the first three days of the disease (Guegan et al., 2006, Pereira et al., 2007, Sekula et al., 2011).

The mortality associated with SJS/TEN can be as high as 35% (de Prost et al., 2010). Local experience mirrors this high mortality with a 2012 South African study reporting a mortality of 24% in patients with $\geq 40\%$ BSA involved (Kannenbergh et al., 2012).

1.3. DRESS

1.3.1. Definition of DRESS

A drug reaction with eosinophilia and systemic symptoms (DRESS) is also known as drug-induced hypersensitivity syndrome (DIHS). It is a severe form of CADR with multi-system involvement. These include fever, a rash, and internal organ involvement that can manifest as hepatitis, haematological abnormalities and systemic illness (Myers et al., 1937, Criado et al., 2012, Pinana et al., 2010). Myers and colleagues first described reported DHIS as an exfoliative dermatitis caused by sulphanilamide in 1937. Thirteen years later, Chaiken et al. reported systemic complications such as lymphadenopathy and visceral involvement (Chaiken et al., 1950). Later, it became defined by the drugs causing the condition such as phenytoin hypersensitivity and allopurinol hypersensitivity syndrome (Chen et al., 2013). After Vittorio and Muglia reported a rash, fever and lymphadenopathy caused by carbamazepine, the term ‘anticonvulsant hypersensitivity syndrome’ (AHS) was introduced (Vittorio and Muglia, 1995). The anticonvulsant hypersensitivity syndrome was superseded by the term ‘drug-induced hypersensitivity syndrome’ (DIHS) or more simply ‘hypersensitivity syndrome’ (HSS) after reports that other drugs such as sulphonamides, allopurinol and more recently, antiretrovirals, could cause a similar collection of symptoms (Callot et al., 1996). In 1996 Bocquet et al., introduced a new term, “drug rash with eosinophilia and systemic symptoms” (DRESS). The patients presented with fever, infiltrated papules or an exfoliative dermatitis, facial oedema and systematic organ involvement. Systemic features included lymphadenopathy, hematologic abnormalities (hypereosinophilia, atypical lymphocytes), hepatitis,

carditis, interstitial nephritis or interstitial pneumonitis in the first 2 months after the initiation of the drug (Bocquet et al., 1996). In high HIV-burden settings, DRESS has been reported as a form of immune reconstitution inflammatory syndrome (Shiohara et al., 2010).

1.3.2. DRESS epidemiology

The estimated incidence of DRESS ranges between 1 in 1000 and 1 in 10,000 exposures to anticonvulsants (phenytoin, phenobarbital, and carbamazepine) and sulphonamides (Shear and Spielberg, 1988). The incidence is higher in HIV-infected persons (Morar et al., 1999, Munyao et al., 2007, Roujeau, 2005, Salami et al., 2012). A prevalence of 0.07 cases per thousand is described, amongst hospitalized Chinese patients (Li and Ma, 2006).

1.3.3. DRESS pathogenesis

The pathogenesis of DRESS is not fully understood. An immunologic hypersensitivity reaction, genetics (HLA and drug metabolising enzymes) and co-infections have all been postulated to play a role.

1.3.3.1. Immunologic hypersensitivity reaction

It has been suggested that DRESS is a type IV or delayed type hypersensitivity reaction. This is supported by the long incubation period before onset of symptoms and the more rapid recurrence of symptoms on re-exposure to the drug (Chen et al., 2013).

1.3.3.2. Drug metabolism

There is some evidence that the defective metabolism of drugs or impaired renal clearance results in building up of reactive metabolites. This is associated with a higher incidence and severity of DRESS (Bohan et al., 2007, Chen et al., 2013, Chung et al., 2014).

1.3.3.3. Viral Infection

Sequential reactivation of the herpesvirus family appears to have a significant role in the condition. Data from Japan associated DRESS show early reactivation of human herpesvirus (HHV) 6 and Epstein Barr virus (EBV), with the later involvement of HHV 7 and cytomegalovirus (CMV) (Shiohara et al., 2006). Aihara et al., postulate that in susceptible people, a transient drug-induced hypo-gammaglobulinaemia creates an immunological environment that permits viral reactivation of HHV 6 (Aihara et al., 2003). This is associated with prolonged and more severe disease.

1.3.3.4. Genetic predisposition

HLA-B*5801 has been demonstrated as a predictor and genetic marker for DRESS caused by allopurinol (Hung et al., 2005). Abacavir hypersensitivity is immunologically mediated by conventional MHC-I antigen presentation and activation of HLA-B*5701 allele. This results in CD8+ T cells mediated cytotoxicity (Chessman et al., 2008).

1.3.4. DRESS clinical features

DRESS typically presents with fever, rash, lymphadenopathy, leucocytosis and abnormal liver tests. There may be a clinical overlap with other severe drug eruption syndromes, such as SJS/TEN (Criado et al., 2012, Roujeau and Stern, 1994, Gentile et al., 2010, Criado et al., 2004, Ganeva et al., 2008, Chen et al., 2010). An urticarial, maculopapular eruption associated with cutaneous oedema is reported most often, but vesicles, bullae, pustules, cheilitis, conjunctivitis, purpura, target lesions and erythroderma have also been described (Figure 9) (Peyriere et al., 2006, Eshki et al., 2009).



Figure 9. A drug reaction with eosinophilia and systemic symptoms: scale, facial oedema, erythema and cheilitis

Due to the delayed onset after starting the medication and the variable cutaneous presentation and systemic involvement, diagnosing DRESS is often difficult. Facial oedema, which is sometimes gross and mistaken for angioedema is typical of DRESS. Although the eruption of DRESS is extensive and symptomatic, the major morbidity in DRESS arises from visceral involvement: fever (usually $>38^{\circ}\text{C}$), lymphadenopathy, haematological abnormalities (most often eosinophilia and atypical lymphocytosis) and involvement of at least one other internal organ system (especially the liver, but also the kidneys, lungs and heart). Liver disturbance occurs in most cases with either hepatocellular or cholestatic damage, and in severe cases

fulminant hepatic failure may necessitate liver transplantation. Any organ in the body can be involved in the hypersensitivity inflammatory reaction, including the thyroid, pancreas and brain. It is suggested that DRESS is more frequent among person of African ancestry. The mortality rate from carbamazepine and phenytoin DRESS has been estimated at 10%. (Walsh and Creamer, 2011, Peyriere et al., 2006).

1.3.5. Long-term complications

Patients with DRESS have a wide variety of complications as a consequence of the multiple organs involved during the course of the disease. These may develop long after resolution of the cutaneous eruption. Several studies have shown that autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroid disease may develop within a year after resolution of the symptoms of DRESS (Aota et al., 2009, Aota and Shiohara, 2009, Brown et al., 2009, Chiou et al., 2006, Kano et al., 2007, Seino et al., 2004, Sommers and Schoene, 2002). A Japanese study found a high prevalence of autoantibodies in the late phase of the disease. These may be associated with subsequent development of autoimmune diseases such as systemic lupus erythematosus (Ushigome et al., 2013).

1.3.5.1. Type 1 diabetes mellitus (DM)

Recent studies suggest that the incidence of type 1 DM is higher in people who have had DRESS, usually developing between three weeks and 10 months after the resolution of the clinical symptoms of DRESS. This often follows a fulminant course (Kano et al., 2015, Onuma et al., 2012).

1.3.5.2. Thyroid Dysfunction/Thyroiditis

In rare cases, patients with DRESS develop thyroid dysfunction and later on some develop autoimmune thyroid disease. The reported lag period between the two diseases ranges between 3 months to 1 year. In comparison to the general population, antithyroid antibodies are detected more frequently in cases of DRESS even in the absence of clinical manifestations of thyroid disease (Brown et al., 2009, Kano et al., 2015).

1.3.6. Management

Treatment of DRESS is mainly supportive. It can be treated with topical or oral corticosteroids (Eshki et al., 2009). Some cases persist for prolonged periods, often associated with herpes virus re-activation. Immunosuppressant agents, such as cyclosporine, are seldom warranted (Zuliani et al., 2005, Harman et al., 2003).

1.3.7. Prognosis

DRESS associated mortality in HIV is poorly described. An estimated mortality of 10-20% for DRESS has been reported in an HIV uninfected cohort (Myers et al., 1937, Criado et al., 2012, Pinana et al., 2010). The most common causes of death in DRESS are liver failure and sepsis (Chen et al., 2010). Most cases of DRESS recover completely, but some may develop long-term sequelae, especially autoimmune diseases and permanent end-organ failure (Chen et al., 2013, Ghislain and Roujeau, 2002).

1.4. Anxiety and depression in the general population of Lower and Middle Income Countries (LMICs)

There are few epidemiological studies on common mental disorders conducted in the sub-Saharan African countries. Gureje et al., (2006) found an estimated prevalence of major depressive disorder of 3.3% among 4984 Nigerians. The study utilized the World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) (Gureje et al., 2006). Among a Ugandan sample of 600 from the Masaka and Rakai districts of southwest Uganda, 21% were depressed, according to the Diagnostic and Statistical Manual IV (DSMI IV) (Bolton et al., 2004). In neighbouring Rwanda the estimated prevalence of major depressive disorder was 15.5% (Bolton et al., 2002). In a cohort of 4351 adult South Africans of all ethnic groups, anxiety was found in 15.8% and 9.8% had mood disorders (Herman et al., 2009, Stein et al., 2008). This was a household survey over a period of two years

using the World Health Organization Composite International Diagnostic Interview (WMH-CIDI) tool to generate diagnoses. The Western Cape had the highest 12-month and lifetime prevalence rates. The prevalence of depression amongst 242 pregnant women from a rural settlement of northern KwaZulu-Natal, South Africa undergoing routine HIV testing was 41% using the Edinburgh Postnatal Depression Scale (Rochat et al., 2006).

1.5. Anxiety and depression in HIV-infected patients in LMICs

Disorders such as major depression and generalized anxiety disorder appear to be common among patients with HIV (Berger-Greenstein et al., 2007). Two-thirds of the world's HIV-infected population lives in sub-Saharan Africa yet few studies have assessed the prevalence of anxiety and depression in the region. Such studies have been identified as a global priority (WHO, 2008). In a Tanzanian study depression or mixed anxiety and depression was found in 15.5% of 220 HIV-infected subjects diagnosed via the Clinical Interview Schedule-Revised questionnaire (Marwick and Kaaya, 2010).

Martinez et al., reported a 19% prevalence of depressive symptoms among 432 Ugandan HIV-infected people (Martinez et al., 2008). Depressive symptoms were assessed with the depression section of the Hopkins Symptoms Checklist (DSHSCL). Olley et al., reported that among 149 South African HIV-infected patients (44 males, 105 females) attending a tertiary infectious diseases clinic in Cape Town, 34.9% had major depression while 21.5% had a dysthymic disorder as assessed by the Mini-International Neuropsychiatric Interview (Olley et al., 2003). In a six-month

follow-up study of this sample, 26% of the subjects continued to meet the criteria for depression. This was significantly associated with disability in work/social/family functioning, greater number of negative life events, and a decline in CD4 lymphocyte count. Of those patients with depression at baseline, 55.1% improved. However, 8.1% new onset depression was found at the six months follows up (Olley et al., 2006). Freeman et al., found a 11% prevalence of major depressive disorder among 900 South African HIV-infected people by using the Composite international diagnostic inventory (CIDI) (Freeman et al., 2007). A year later, a 14% prevalence of depression in 465 patients enrolled in HIV care and treatment services in Cape Town, South Africa were reported (Myer et al., 2008).

There is also some evidence that depression in patients with HIV-infection is independently associated with poor adherence to medication, even in patients with no background of severe drug reactions (Mayston et al., 2012).

1.6. Anxiety and depression in HIV-positive versus HIV-negative population

Hughes et al., conducted a comparison study of 231 HIV/AIDS subjects eligible for HAART, but not yet commenced on treatment with 108 HIV negative randomly selected controls from the community of the isiXhosa speaking residents of Khayelitsha, Cape Town, South Africa (Hughes et al. (2004). They found that among the HIV-infected patients, 33.4% reported symptoms of anxiety and depression, compared with 24.2% in the randomly selected community sample.

1.7. Anxiety and depression in hospitalized patients

Admission to critical care is associated with anxiety and depression (Pattison (2005). A systematic review of studies was undertaken to explore the association between depression or depressive symptoms, hospitalization and related outcomes. The meta-analysis of seven studies found that depressive symptoms might increase the risk of subsequent admission to a general hospital (RR=1.36, 95% CI: 1.28-1.44) (Prina et al., 2015). Prina and Wong independently reported that depressive symptoms were associated with an increased number of re-hospitalizations (Prina et al., 2013, Wong et al., 2009).

1.8. Anxiety and depression in Adverse Drug Reactions

Gutierrez-Islas et al., from Santa Maria Benquerencia Health Center, Spain, conducted a retrospective case control study of 108 cases of patients who reacted to anti-inflammatory drugs (32), antibiotics (34) cases and drugs that acted on the nervous system (51) in compared to 203 control patients without any adverse drug reactions. They found that 45.5 % of cases had a history of anxiety and 41.7 % had a history of depression, compared to 19.7% and 15.3 %, respectively, of the controls. Older women with chronic conditions and polypharmacy were most affected (Gutierrez-Islas et al., 2012).

1.9. Anxiety and depression in SJS/TEN sequelae

We found no epidemiologic studies that evaluated the incidence and prevalence of mental health in patients with SJS/TEN sequelae.

1.10. Anxiety and depression in DRESS sequelae

Epidemiologic studies designed to evaluate the incidence and prevalence of DRESS have not attempted to analyse the direct association between DRESS, sequelae and mental health. However, a complication of DRESS such as diabetes has been shown to be associated with anxiety and depression (Onuma et al., 2012, Kano et al., 2015). Thyroid dysfunction has a higher frequency of hypothyroidism and patients with hypothyroidism have a higher occurrence of depressive symptoms (Duntas and Maillis, 2013).

1.11. Instruments available to assess depression and anxiety

1.11.1. Centre for Epidemiological Studies Depression Scale (CES-D) is a 20 item self-reported scale, which measures the current level of depressive symptomatology in the general population, with an emphasis on depressed mood during the past week (Radloff, 1977). The scale is derived from five validated depression scales, including the Beck Depression Inventory (BDI). CES-D has been validated in community and primary care populations. Scores range from 0 to 60, with higher scores indicating more symptoms of depression. CES-D scores of 16 to

26 are considered indicative of mild depression and scores of 27 or more indicative of major depression. A cut-off score of 27 has been found to be more useful for screening, medical patients for depression than the standard cut-off score of 16 (Zich et al., 1990).

1.11.2. The Beck Depression Inventory, version 2 is an instrument for measuring the severity of depression in psychiatric patients. It is recognized as a 'gold standard' among self-report measures of depression. It was originally developed in 1967, was updated in 1996 to correspond to the revised diagnostic criteria for depressive disorders as listed in the *Diagnostic and Statistical Manual of Mental Disorders 4th Edition* (DSM-IV). It is a 21-item scale, with possible scores ranging from 0 to 63 (higher values correspond to higher depressive symptomatology). Scores are interpreted in ranges: not depressed (0-13); mild depression (14-19); moderate depression (20-28); and severe depression (29-63) (Steer et al., 1999).

1.11.3. The Hospital Anxiety and Depression scale (HADS) is the most widely utilised and a validated scale for screening anxiety and depression in hospitalized patients. Using the self-report HADS to assess patients at baseline and designated follow-up intervals is an accurate and reliable strategy that allows identification of those individuals who are at risk for anxiety and depression and who require further intervention or consultation. Patients can complete and score the questionnaires themselves in the consultation room.

Zigmond and colleagues developed the HADS, to identify cases (possible and probable) of anxiety and depression among patients in non-psychiatric hospitals. This was specifically designed to avoid reliance on aspects of these conditions that

are also common somatic symptoms of illness, for example fatigue and insomnia or hypersomnia (Zigmond and Snaith, 1983). HADS was designed as a tool for the detection of anxiety and depression in people with physical health problems. The score seems to have at least as good screening properties as similar but more comprehensive instruments, used for identification of anxiety and depression. HADS has been validated in a number of settings (Bjelland et al. (2002). HADS has been shown to perform well as a screening tool to measure anxiety and depression in non-psychiatric hospital patients and is considered to be free of bias from co-existing general medical conditions (Snaith, 1987, Bjelland et al., 2002). It has been used in patients suffering from hypertrophic cardiomyopathy in a clinic at St. George's Hospital and Medical School in London (Poole and Morgan, 2006).

HADS is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression symptoms. Each item is coded from 0 to 3. The scores for anxiety and depression can therefore vary from 0 to 21, depending on the presence and severity of the symptoms. For both the anxiety (HADS-A) and the depression (HADS-D) subscales, a score of 0-7 can be regarded as within a normal range (no case), while a score ≥ 11 indicates a probable case; scores between 8 and 10 are doubtful cases.

To describe all scenarios of anxiety and depression the following definitions are used: for anxiety: non-case [A^{-1}], borderline case [A^0] and definite case [A^{+1}]; for depression: non-case [D^{-1}], borderline case [D^0], and definite case [D^{+1}].

Using the above definitions, five subgroups were defined by Demyttenaere and colleagues from broadly used DSM-IV diagnostic categories

(Demyttenaere et al., 2009):

1. Non-caseness: $D^{-1} A^{-1}$, $D^{-1} A^0$ or $D^0 A^{-1}$
2. Caseness for anxiety: $D^{-1} A^{+1}$ or $D^0 A^{+1}$
3. Caseness for depression: $D^{+1} A^{-1}$ or $D^{+1} A^0$
4. Caseness for comorbid anxiety-depression: $D^{+1} A^{+1}$
5. Mixed anxiety-depression: $D^0 A^0$ (sub threshold depressive and anxious symptomatology).

CHAPTER 2: STUDY AIMS AND OBJECTIVES

2.1 STUDY AIMS and OBJECTIVES

Hypothesis

We hypothesised that Severe Cutaneous Adverse Drug Reactions (SCADR) predispose patients to anxiety and depression.

Aim

Our study aimed to prospectively investigate the presence of anxiety and depression in patients with SCADR, as well as assess their quality of life at two time intervals, using validated scoring systems. Specifically, four objectives were pursued to achieve this:

- Determine the prevalence of anxiety and depression in patients with SCADR after resolution of the acute stage of illness at six weeks
- Determine whether anxiety and depression in patients with SCADR is associated with the severity of the disease
- Determine whether anxiety and depression in patients with SCADR is sustained beyond resolution of the acute stage
- Determine the impact of SCADR on quality of life

2.2. MATERIALS and METHODS

2.2.1. Study population and recruitment

Patients with SCADR admitted to Groote Schuur Hospital, Cape Town, between April 2012 and September 2013 were recruited. Only patients with a diagnosis of SJS, SJS-TEN, TEN (blistering drug reaction disorders) or DRESS were eligible for this prospective observational study.

No patients receiving treatment for or with a history of premorbid anxiety and depression were eligible. No measurement of depression and anxiety symptoms prior to admission with the drug reaction was possible.

This was a descriptive study of anxiety and depression in a SCADR population, a group that has not previously been evaluated. No control group was recruited due to anticipated time constraints and difficulties recruiting a comparator group who were HIV-infected with a similar prolonged hospital stay.

Inclusion criteria:

- Subjects above the age of 18 who were willing and able to give consent,
- Subjects diagnosed with SJS/TEN and DRESS who warranted admission to hospital,

- Subjects who were willing and able to answer the questionnaires on two occasions.

Exclusion criteria

- Patients unable to come for follow-up
- Patients with psoriasiform, morbilliform or lichenoid drug eruptions, fixed drug eruption (FDE), urticaria, cutaneous vasculitis or acute generalized exanthematous pustulosis irrespective of requiring hospital admission.
- Patients unwilling to sign consent
- Patients unable to read and answer the self-administered questionnaires
- Patients with depression and/or anxiety prior to developing SCADR

2.2.2. Instruments

The following instruments were used to assess all subjects.

2.2.2.1. The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (Appendix 5), a self-administered scale was utilised to measure anxiety (HADS-A) and depression (HADS-D) scores. It consists of 14 items, in which subjects are required to answer, 'no, not at all' 'no, not much', 'yes sometimes', 'yes, definitely' denoted by a scale of 0-3, indicating the strength of agreement with each item. For both

conditions, a score between 0 and 7 is regarded as normal, a score ≥ 11 indicates a definite case and a score between 8 and 10 is a borderline case (Zigmond and Snaith, 1983).

Patients were categorised into cases and non-cases of anxiety and depression using the following categories as defined by Demyttenaere and colleagues (Demyttenaere et al., 2009):

1. Non-caseness: $D^{-1} A^{-1}$, $D^{-1} A^0$ or $D^0 A^{-1}$
2. Caseness for anxiety: $D^{-1} A^{+1}$ or $D^0 A^{+1}$
3. Caseness for depression: $D^{+1} A^{-1}$ or $D^{+1} A^0$
4. Caseness for comorbid anxiety-depression: $D^{+1} A^{+1}$
5. Mixed anxiety-depression: $D^0 A^0$ (sub threshold depressive and anxious symptomatology)

Cases of anxiety and/or depression at six weeks and still meeting the criteria for anxiety and/or depression at six months were referred as persistent cases (Demyttenaere et al., 2009).

2.2.2.2. The Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) (Appendix 6), a validated self-administered questionnaire of 10 questions, each scored on a 4-point Likert scale (0-3), concerning the patients' perception of the impact of the skin diseases on different aspects of their life, for dermatological patients over the

age of 16 years. The DLQI consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment. Each question is answered by a ticked box: "very much", "a lot", "a little" and "not at all".

Each question is scored from 0 to 3 and the scores summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment) The scoring of each question is as follows: Very much = 3, A lot = 2, a little = 1, not at all = 0, not relevant scored 0 and question 7, prevent work and studying = 3. A score between 0 and 1 is regarded as no effect at all on patient's life, 2 and 5 small effect on patient's life, 6 and 10 moderate effect on patient's life, 11 and 20 very large effect on patient's life and 21 and 30 extremely large effect on patient's life. All questions relate "to the last week" (Finlay and Khan, 1994, Basra et al., 2008).

The two instruments were translated into Afrikaans and isiXhosa. Different translators, to ensure that the original meaning was retained, back translated them into English.

2.2.3. Data collection

Patients admitted to the hospital with severe cutaneous adverse drug reaction (SCADR) were screened for inclusion criteria. An informed written consent was administered to all qualifying patients before enrolment into the study. Demographic data were recorded. Drug history, including precipitating

therapeutic agents and concomitant medications was documented. Human immunodeficiency virus (HIV) status as confirmed by laboratory testing was recorded. Patients testing positive for HIV had their CD4 cell counts done.

The cutaneous findings and the clinical diagnosis as determined by the attending clinician at both initial presentation and subsequent follow-up were recorded.

The instruments for assessing study outcomes (HADS and DQLI) were administered by one of the co-investigators or a trained nurse in the patient's preferred language. These were administered at six weeks post discharge and again at the six months follow up visit. To reduce loss to follow up, each patient was contacted and reminded of the follow-up appointment closer to the date. All the patients who reported suicidal ideation at any time following onset of SCADR were referred for psychiatric intervention and treatment.

All data as recorded on a paper case report form were entered into a Microsoft Excel spread sheet and later exported to Stata statistical package for analysis.

2.2.4. Statistical analysis and data presentation

Categorical variables were summarized as percentages while continuous variables were reported as medians with interquartile range (IQR). Summary statistics were calculated for the outcomes of interest for each visit.

All statistical analyses were conducted using Stata Statistical Software (Release 13. College Station, TX: StataCorp LP).

2.2.5. Source of funding

This study was self-funded.

2.2.6. Ethics

Ethics approval for this study was obtained from the University of Cape Town Human Research Ethics Committee (HREC/REF: 059/2012) and complied with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from each individual before data collection.

CHAPTER 3: STUDY RESULTS

3.1. RESULTS

3.1.1. Participants at six weeks

Fifty patients with SCADR admitted to Groote Schuur Hospital, Cape Town, between April 2012 and September 2013 were recruited. All forty-eight patients with a diagnosis of SJS, SJS-TEN, TEN (blistering drug reaction disorders) or DRESS were eligible for this prospective observational study. Two patients, one with urticaria and one with a generalised bullous fixed drug reaction were excluded (Figure 10). None of the patients with SCADR had premorbid anxiety and/or depression and none were receiving treatment for either condition. Actual measurement of depression and anxiety symptoms prior to admission with a drug reaction was not possible.

Of the 48 enrolled patients [median age 35 (IQR 28-42) years], 38 were black African and 10 were of mixed ancestry. The majority were female (n = 35, 73%) and HIV infected (n = 39, 81%) with a median CD4 count of 262 (IQR 149 - 380) cells/mm³.

In total 34 patients were categorized as SJS/TEN, 23 patients were categorized as SJS [median age 34 (IQR 28-37) years], eight as TEN [median age 25 (IQR 36-43) years], three as SJS-TEN overlap (34, 37 and 47 years of age)]. Fourteen of the patients were diagnosed with DRESS [median age 36 (IQR 28-44) years]. The demographic of the patients are shown in Table 1. The raw data for each patient are reflected in Appendix 7.

Post-inflammatory hyperpigmentation (PIHP) was the most common sequelae at six weeks, seen in 88% (42/48) of the patients. This included all the patients with SJS/TEN (34/34). For patients with DRESS, 8/14 (57%) had PIHP. After PIHP, nail dystrophy (21/34, 62%) and dry eye syndrome (3/34, 9%) were the commonest cutaneous sequelae.

Forty-eight HADS and DQLI questionnaires were completed at six weeks and 37 of the 48 (77%) questionnaires were completed at the six months follow up. All 85 questionnaires were analysed.

Table 1 and Figure 10 reflect the demographics of the patients at six weeks and six months and those lost to follow-up. The demographics are similar in both groups apart from ethnicity as fewer of the mixed ancestry origin patients returned for the 6 months' follow-up. One of the patients with SJS and suicidal ideation died from co-morbid disease, not suicide.

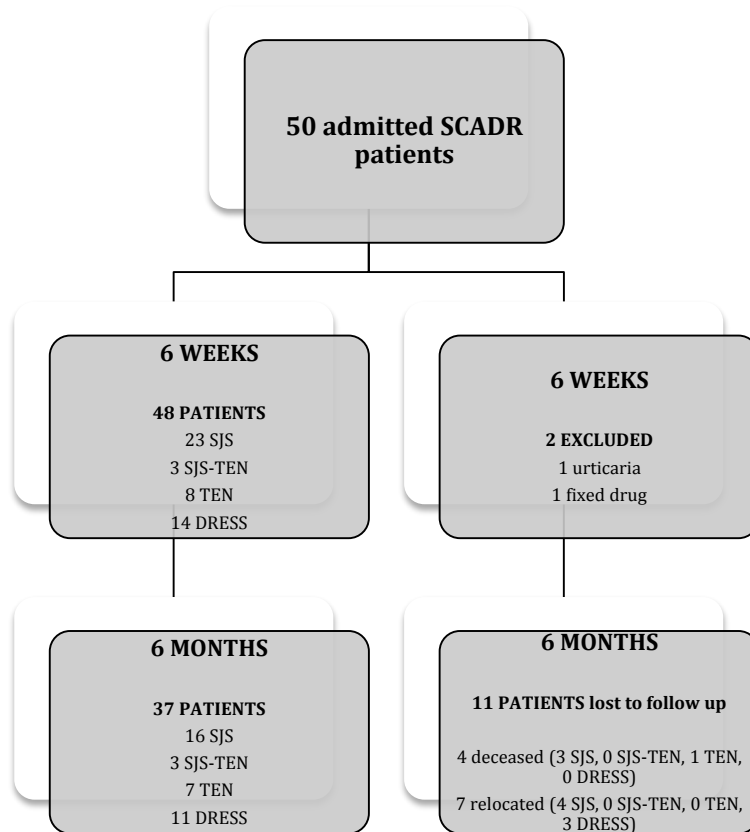


Figure 10: Flow chart of eligible recruited and lost to follow-up of patients

Table 1. Demographics of patients at six weeks and six months

	Six weeks	Six months
Classification (score)	Demographics (n = 48)	Demographic (n = 37)
Age	Median age 35 (IQR 28-47)	Median age 35 (IQR 28 -44)
Gender		
Male	13 (25%)	8 (22%)
Female	35 (75%)	29 (78%)
Ethnicity		
African	38 (79%)	34 (92%)
Mixed race	10 (21%)	3 (8%)
HIV-infected	39 (81)	34 (92)

CD4 cell count (cells/mm³)	262 (IQR 149 - 380)	262 (IQR 149 - 380)
Sequelae		
Dyspigmentation	42 (88)	22 (85)
Nail dystrophies	21 (62)	21 (45)
Ocular complication	3 (9)	3 (12)
Type of SCADR		
DRESS	14 (29%)	11 (30%)
SJS	23 (48%)	16 (43%)
SJS-TEN	3 (6%)	3 (8%)
TEN	8 (17%)	7 (19%)
Classification (HADS score)		
Anxiety	2 (4)	0 (0)
Depression	2 (4)	3 (8)
Co-morbid A-D	19 (40)	13 (35)
Mixed A-D	0 (0)	1 (3)
Non-case	25 (52)	20 (54)
DLQI (score)		
No effect (0-1)	14 (29%)	13 (35%)
Small effect (2-5)	12 (25%)	5 (14%)
Moderate effect (6-10)	1 (2%)	3 (8%)
Large effect (11-20)	13 (27%)	7 (19%)
Extreme effect (21=30)	7 (15%)	7 (19%)
Not done	1 (2%)	2 (5%)
Lost to follow up	0	7
Deceased	0	4

IQR = Interquartile range, DRESS = drug reaction with eosinophilia and systemic symptoms, SJS = Steven Johnson syndrome, SJS-TEN = Steve-Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis, HADS = Hospital Anxiety and Depression Scale, Co-morbid A-D = Co-morbid anxiety-depression, Mixed A-D = Mixed anxiety-depression, n = number of patients, DLQI = The Dermatology Life Quality Index

3.1.2. SCADR patients with cases of anxiety at six weeks

Based on the HADS score 8/14 (57%) patients with DRESS [median HADS score 2.5 (IQR 0-5.75)] were not anxious, 1/14 (7%) (HADS score 10) had borderline anxiety and 5/14 (36%) [median HADS score 14.5 (IQR 10.75-18)] were classified as cases of anxiety.

Fifteen of the thirty-four (44%) patients with SJS/TEN [median HADS score 4 (IQR 3-5)] did not have anxiety, 4/34 (12%) [median HADS score 9 (IQR 8-10)] were borderline cases while 15/34 (44%) [median HADS score 16 (IQR 12-17)] were cases of anxiety.

Of the 23 SJS patients, 10 (43.5%) [median HADS score 3.5 (IQR 2.25-5.25)] did not have anxiety, three (13%) [HADS scores 8, 8 and 10] were borderline cases and the other 10 (43.5%) [median HADS score 15.1 (IQR 11-18)] were cases of anxiety. Four of the eight (50%) patients with TEN [median HADS score 4.5 (IQR 3.25-5.75)] were normal cases, while four of the eight (50%) [median HADS score 15.5 (IQR 13-17)] were cases of anxiety. There were no borderline cases. One of the three (33.3%) (HADS score 0) patient with SJS-TEN overlap had no anxiety, one (33.3%) (HADS score 10) was a borderline case and one (33.3%) (HADS score 15) was a case of anxiety.

In total, anxiety or borderline anxiety symptoms/caseness was identified in 25/48 (52%) patients with SCADR [median HADS score 14 (IQR 11-17)].

These included, six (43%) patients with DRESS, 13 (57%) patients with SJS, two (66.7%) patients with SJS-TEN overlap and four (50%) patients with TEN (see Table 2).

3.1.3. SCADR patients with cases of depression at six weeks

Based on the HADS score 7/14 (50%) patients with DRESS [median HADS score 2.4 (IQR 0-3)] were not depressed and 7/14 (50%) [median HADS score 14.2 (IQR 13-15)] were cases of depression. There were no borderline cases.

Seventeen of the thirty-four (50%) patients with SJS/TEN [median HADS score 4.8 (IQR 3.5-6)] had no depression, two of the 34 (6%) (HADS scores 8 and 9) were borderline cases and 15/34 (44%) [median HADS score 14.4 (IQR 12-17)] were cases of depression.

Of the 23 SJS patients, 12 (52%) [median HADS score 4 (IQR 3.25-6)] had no depression, one of the 23 (4%) (HADS score 11) was a borderline case and 10/23 (44%) depression cases [median HADS score 14.9 (IQR 11.75-17.25)] respectively. Three of the eight (37.5%) patients with TEN had no depression, one (12.5%) (HADS score 8) was a borderline case and depression was recorded in four (50%) of TEN patients compared to one (33.3%) patient with SJS-TEN overlap.

Depression or borderline depression symptoms/caseness was identified in 24/48 (50%) patients with SCADR [median HADS score 14 (IQR 12-16.5)]. These included, seven (50%) patients with DRESS, 11 (48%) with SJS, one (33.3%) patient with SJS-TEN overlap and five (63%) patients with TEN (see Table 3).

3.1.4. SCADR patients with cases of comorbid anxiety and depression at six weeks

Based on the HADS score 7/14 (50%) patients with DRESS [median HADS score 2.4 (IQR 0-5.75)] were non-caseness, 2/14 (14%) (HADS score 12 and 10) had pure depression and 5/14 (36%) [median HADS score 14.5 (IQR 0-17)] were classified a cases of comorbid anxiety and depression.

Seventeen of the thirty-four (50%) patients with SJS/TEN [median HADS score 5 (IQR 3-5)] were non-caseness, 2/34 (6%) (HADS score 9.5 and 5.5) had pure depression, 2/34 (6%) (HADS score 8 and 9) had pure anxiety while 13/34 (38%) [median HADS score 15 (IQR 0.75 – 19.25)] were cases of comorbid anxiety and depression.

Of the 23 SJS patients, 11 (47.8%) [median HADS score 4.75 (IQR 2.25-5.25)] did not have comorbid anxiety and depression, two (9%) [HADS scores 9.5 and 5.5] had pure depression and two (9%) (median HADS score 8 and 9) had pure anxiety (9%), while 8 (35%) [median HADS score 15.3 (IQR 0.75-16.25)] were cases of comorbid anxiety and depression. Four of the eight (50%) patients with TEN [median HADS score 6 (IQR 3.25-5.75)] did not have comorbid anxiety and depression, while four of the eight (50%) [median HADS score 15 (IQR 13-17)] were cases of comorbid anxiety and depression. There was no pure depression or pure anxiety. Two of the three (66.7%) (HADS score 8.5 and 1) patients with SJS-TEN overlap had no comorbid anxiety and depression, no pure depression or pure anxiety while one (33.3%) (HADS score 13) was a comorbid anxiety and depression.

In total, comorbid anxiety and depression symptoms/caseness was identified in 18/48 (38%) patients with SCADR [median HADS score 15 (IQR 12.87-17.63)]. These included, five (36%) patients with DRESS, 8 (35%) patients with SJS, one (33.3%) patient with SJS-TEN overlap and four (50%) patients with TEN (see Table 4).

3.1.5. SCADR patients and quality of life at six weeks

Overall 14/48 (29%) of SCADR patients did not have their quality of life affected by their illness at 6 weeks. Twelve of the forty-eight (25%) were slightly affected, 1/48 (2%) was moderately affected and 14/48 (29%) were very largely affected and 11/48 (23%) were extremely affected. On further break down, 5/14 (36%) of DRESS patients had a normal DLQI while 2/14 (14%) were slightly affected, 5/14 (36%) were very largely affected and 2/14 (14%) were extremely affected. Nine of the thirty-four (27%) of SJS/TEN patients had a normal DLQI while 10/34 (29%) were slightly affected, 1/34 (3%) was moderately affected, 9/34 (27%) were very largely affected and 7/34 (21%) were extremely affected.

Of the 34 patients with SJS/TEN, 7/23 (30.4%) of SJS patients had a normal DLQI while 7/23 (30.4%) were slightly affected, 1/23 (4.4%) was moderately affected, 4/23 (17.4%) were very largely affected and 4/23 (17.4%) were extremely affected. One of the eight (12.5%) patient of TEN had a normal DLQI while 2/8 (25%) were slightly affected, 4/8 (50%) were very largely affected and 1/8 (12.5%) were extremely affected, 1/3 (33.3%) of SJS-TEN

overlap patient had a normal DLQI, 1/3 (33.3%) were slightly affected and 1/3 (33.3%) extremely affected. The patients and corresponding DLQI score are shown in Table 5.

3.1.6. Participants at six months

Out of the initial cohort of 48 patients, 11 (23%) were not reviewed in six months. Four of them had died in the interim while the other seven relocated from the Western Cape Province. A total of 37 patients [median age 35 (IQR 28-42) years] were reviewed again at 6 months, 34 of whom were of black African and three of mixed ancestry. The majority were female (n = 29, 78%) and HIV infected (n = 34, 92%) with a median CD4 count of 262 (IQR 149 - 380) cells/mm³. In total, 16 patients were categorized as SJS [median age 35 (IQR 28-42) years], seven with TEN [median age 25 (IQR 36-43) years], three with SJS-TEN overlap (34, 37 and 47 years of age). Eleven of the patients were diagnosed with DRESS [median age 36 (IQR 28-44)]. The characteristics of each patient are shown in Table 1.

As at 6 weeks, PIHP was the most common sequelae noted in 22/26 (85%) patients with SJS/TEN and 5/11 (45%) of DRESS. This was followed by nail dystrophy of 21/26 (81%) and dry eye syndrome of 3/26 (12%) of the patients with SJS/TEN.

3.1.7. SCADR patients with cases of anxiety at six months

Based on the HADS score 7/11 (64%) patients with DRESS [median HADS score 1 (IQR 0-4)] were not anxious, 2/11 (18%) had borderline anxiety, 2/11 (18%) were classified as cases of anxiety. Three of the original fourteen (21%) patients of DRESS were lost to follow-up.

Eleven of the twenty-six (42%) patients of SJS/TEN [median HADS score 3 (IQR 2-4)] had no anxiety, 3/26 (12%) were borderline anxiety, 11/26 (42%) [median HADS score 15 (IQR 13-18)] were cases of anxiety. Eight of the thirty-four (24%) patients with SJS/TEN were lost to follow-up.

Of the 16 SJS patients, seven (43.75%) [median HADS score 3 (IQR 2-6)] had no anxiety, two (12.5%) [HADS scores 8 and 9] were borderline cases. Seven (43.75%) [median HADS score 18 (IQR 13-19)] were cases of anxiety. Three of the seven patients with TEN (43%) (HADS scores of 3, 4 and 4) had no anxiety, one (14%) (HADS score of 8) borderline case and three (43%) (HADS scores 14, 16 and 17) were cases of anxiety. Two of the three (66.7%) (HADS score of 2) patients with SJS-TEN overlap had no anxiety, one (33.3%) was anxious and there were no borderline cases.

In total, anxiety or borderline anxiety symptoms/caseness was identified in 19/37 (51%) patients with SCADR [median HADS score 13 (IQR 9 -17.5)]. These included four (36%) patients with DRESS, nine (56%) patients with SJS, four (57%) patients with TEN and two (66.7%) patients with SJS-TEN overlap (see Table 2).

3.1.8. SCADR patients with cases of depression at six months

Based on the HADS score 8/11 (73%) patients with DRESS [median HADS score 1 (IQR 0-5.25)] were not depressed, 3/11 (27%) (HADS scores 13, 15 and 15) were cases of depression and there were no borderline cases. Three of the fourteen (21%) patients with DRESS were lost to follow-up.

Four of the twenty-six (15%) patients with SJS/TEN [median HADS score 1.5 (IQR 0.25-5)] were not depressed, 9/26 (35%) [median HADS score 9 (IQR 8-10)] were borderline cases and 13/26 (50%) [median HADS score 12 (IQR 11-15)] were depressed. Eight of the thirty-four (24%) patients with SJS/TEN were lost to follow-up.

Of the 16 SJS patients, three (19%) had no depression, five (31%) [median HADS score 10 (IQR 8.5-10)] were borderline cases and eight (50%) [median HADS score 12.5 (IQR 11-16.75)] were cases of depression. Four of the seven (57%) patients with TEN [median HADS score 8.5 (IQR 8 - 9)] were borderline cases and three (43%) were cases of depression. One of the three (33.3%) patient with SJS-TEN overlap was not depressed and two (66.7%) (HADS score 11 and 14) were cases of depression and there were no borderline depression.

In total, depression or borderline depression symptoms/caseness was identified in 25/37 (68%) patients with SCADR [median HADS score 11 (IQR 9.5 -14)]. These included, three (27%) patients with DRESS, 13 (81%) patients with SJS, two (66.7%) patients with SJS-TEN overlap and seven (100%) of TEN (see Table 3).

3.1.9. SCADR patients with cases of comorbid anxiety and depression at six months

Based on the HADS score 8/11 (73%) patients with DRESS [median HADS score 2.5 (IQR 0-5.75)] were non-caseness, 2/11 (18%) (HADS score 15 and 13) had pure depression, 1/11 (9%) had pure anxiety [median HADS score 24 and 2/11 (18%) [median HADS score 14 (IQR 0-17)] were classified a cases of comorbid anxiety and depression.

Twelve of the twenty-six (46%) patients with SJS/TEN [median HADS score 4 (IQR 3-5)] were non-caseness, 3/26 (11.5%) (HADS score 12 and 10) had pure depression while 11/26 (42%) patients with SJS/TEN [median HADS score 15.3 (IQR 0.75 – 19.25)] were cases of comorbid anxiety and depression

Of the 16 SJS patients, 8 (50%) [median HADS score 3.5 (IQR 2.25-5.25)] were non-caseness, two (12.5%) [HADS scores 8, 8 and 10] had pure depression, while 6 (37.5%) [median HADS score 15 (IQR 0.75-16.25)] were cases of comorbid anxiety-depression. Three of the seven (43%) patients with TEN [median HADS score 4.5 (IQR 3.25-5.75)] were non-caseness, 1/7 (14%) was mixed anxiety-depression, while three of the seven (43%) [median HADS score 15.5 (IQR 13-17)] were cases of comorbid anxiety-depression.

One of the three (33.3%) (HADS score 0) patients with SJS-TEN overlap were non-caseness and 2/3 (66.7%) (HADS score 10) had no comorbid anxiety and depression.

In total, comorbid anxiety and depression symptoms/caseness was identified in 13/37 (35%) patients with SCADR [median HADS score 15 (IQR 12.75-15.5)]. These included, two (18%) patients with DRESS, 6 (37.5%) patients with SJS, two (66.7%) cases of SJS-TEN overlap and three (43%) cases of TEN (see Table 4).

We found 13/18 (72%) had a high HADS score for co-morbid anxiety and depression with blistering muco-cutaneous disorders [median HADS 15.5 (12.75-17.5)] and 5/18 (28%) DRESS [median HADS 13.5 (IQR 12.75-18)] at six weeks which 9/13 (69%) persisted for the blistering disorders [median HADS 15.5 (IQR 12.75-17.5)] but 1/5 (20%) DRESS (HADS score 18) at six months follow-up.

3.1.10. SCADR patients and quality of life at six months

Overall 15/37 (41%) patients with SCADR did not have their quality of life affected by their illness at 6 months. Five of the thirty-seven (14%) were slightly affected, 4/37 (11%) were moderately affected and 6/37 (16%) were very largely affected and 7/37 (19%) were extremely affected. To further break down, 4/11 (36.4%) of DRESS patients had a normal quality of life while 4/11 (36.4%) were slightly affected, 1/11 (9%) was very largely affected and 1/11 (9%) was extremely affected. Eleven of the twenty-six (42%) of SJS/TEN patients had a normal quality of life while 1/26 (4%) was slightly affected, 3/26 (12%) were moderately affected, 5/26 (19%) were very largely affected and 6/26 (23%) were extremely affected.

Of the 26 patients with SJS/TEN, 9/16 (56%) of SJS patients were slightly affected, 1/16 (6%) was moderately affected, 3/16 (19%) were very largely affected and 3/16 (19%) were extremely affected. One of the seven (14%) patients with TEN had a normal quality of life while 1/7 (14%) was slightly affected, 2/7 (29%) were very largely affected and 2/7 (29%) were extremely affected. One of the three (33.3%) SJS-TEN overlap patients had a normal quality of life and 1/3 (33.3%) was moderately affected, 1/3 (33.3%) was extremely affected. The patients and corresponding DLQI score are shown in Table 5.

3.1.11. SCADR patients with suicidal ideation at six weeks

Five of the forty-eight (10%) patients who reported suicidal ideation were referred for psychiatric intervention and treatment when this was identified at 6 weeks post discharge. All of these patients had SJS with co-morbid depression-anxiety. None of the patients kept their psychiatry appointment. All five patients received psycho-social intervention as standard of care. No medical treatment was given and one of the patients died from co-morbid disease not suicide.

Table 2. Anxiety classification of SCADR patients at six weeks and six months follow-up using the HADS score for anxiety^a

Classification (score)	Six weeks (n = 48)				Six months (n = 37)			
	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)
Case (11+)	6 (43)	10(43.5))	1(33.3)	4 (50)	2 (18)	7 (43.75)	2(66.7)	3 (43)
Borderline case(8-10)	0 (0)	3 (13)	1(33.3)	0 (0)	2 (18)	2 (12.5)	0(0)	1 (14)
Normal case (0-7)	8(57)	10(43.5))	1(33.3)	4 (50)	7 (64)	7 (43.75)	1(33.3)	3 (43)
Total	14 (100)	23(100)	3(100)	8(100)	11 (100)	16(100)	3 (100)	7 (100)

^aHADS = Hospital Anxiety and Depression Scale, SCADR = Severe Cutaneous Adverse Drug Reaction, DRESS = drug reaction with eosinophilia and systemic symptoms, SJS = Steven Johnson syndrome, SJS-TEN overlap = Steven Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis, n = number of patients.

Table 3. Depression classification of SCADR patients at six weeks and six months follow-up using the HADS score for depression^a

Classification (score)	Six weeks (n = 48)				Six months (n = 37)			
	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)
Case (11+)	7 (50)	10(44)	1(33.3)	4 (50)	3 (27)	8 (50)	2(66.7)	3 (43)
Borderline case (8-10)	0 (0)	1 (4)	0(0)	1 (12.5)	0 (0)	5 (31)	0 (0)	4 (57)
Normal case (0-7)	7(50)	12 (52)	2(66.7)	3 (37.5)	8 (73)	3 (19)	1(33.3)	0 (0)
Total	14 (100)	23(100)	3(100)	8(100)	11 (100)	16(100)	3 (100)	7 (100)

^aHADS = Hospital Anxiety and Depression Scale, SCADR = Severe Cutaneous Adverse Drug Reaction, DRESS = drug reaction with eosinophilia and systemic symptoms, SJS = Steven Johnson syndrome, SJS-TEN overlap = Steven Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis, n = number of patients.

Table 4. Caseness classification of SCADR patients at six weeks and six months follow-up using the HADS score for caseness^a

Classification (score)	Six weeks (n = 48)				Six months (n = 37)			
	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)
Anxiety	0 (0)	2 (9)	0(0)	0 (0)	0 (0)	1 (6.25)	0(0)	0 (0)
Depression	2 (14)	2 (9)	0(0)	0 (0)	1 (9)	2 (12.5)	0(0)	0 (0)
Co-morbid A-D	5(36)	8 (35)	1(33.3)	4 (50)	2 (18)	6 (37.5)	2(66.7)	3 (43)
Mixed A-D	-	-	-	-	-	1 (6.25)	-	1 (14)
Non-case	7 (50)	11 (47.8)	2 (66.7)	4 (50)	8 (73)	6 (37.5)	1 (33.3)	3 (43)
Total	14 (100)	23(100)	3(100)	8(100)	11 (100)	16(100)	3 (100)	7 (100)

^aHADS = Hospital Anxiety and Depression Scale, SCADR = Severe Cutaneous Adverse Drug Reaction, DRESS = drug reaction with eosinophilia and systemic symptoms, SJS = Steven Johnson syndrome, SJS-TEN overlap = Steve-Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis, Co-morbid A-D = Co-modird anxiety and depression, Mixed A-D = Mixed anxiety-depression, n = number of patients.

Table 5. Quality of life classification of SCADR patients at six weeks and six months follow-up using the DLQI score^a

Classification (score)	Six weeks (n = 48)				Six months (n = 37)			
	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)	DRESS n(%)	SJS n(%)	SJS-TEN n(%)	TEN n(%)
Extreme large effect (21-30)	2 (14)	4 (17.4)	1(33.3)	1 (12.5)	1 (9)	3 (19)	1 (33.3)	2 (29)
Very large effect (11-20)	5 (36)	4 (17.4)	0(0)	4 (50)	1 (9)	3 (19)	0 (0)	2 (29)
Moderate effect (6-10)	0 (0)	1 (4.4)	0(0)	0 (0)	1 (9)	1 (6)	1(33.3)	1 (14)
Small effect (2-5)	2 (14)	7 (30.4)	1 (33.3)	2 (25)	4 (36.4)	0 (0)	0 (0)	1 (14)
No effect (0-1)	5 (36)	7 (30.4)	1 (33.3)	1 (12.5)	4 (36.4)	9 (56)	1 (33.3)	1 (14)
Total	14 (100)	23(100)	3(100)	8(100)	11 (100)	16(100)	3 (100)	7 (100)

^aDRESS = A drug reaction with eosinophilia and systemic symptoms, SJS = Steve-Johnson syndrome, SJS-TEN overlap = Steve-Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis, n = number of patients.

CHAPTER 4: DISCUSSION

4.1. DISCUSSION

This study investigated the prevalence of anxiety and depression in a cohort of predominantly HIV-infected people, with severe cutaneous adverse drug reactions (SCADR). To our knowledge, this is the first prospective observational study in Africa, to have used a validated questionnaire to describe the mental health status of a cohort with SCADR who are largely HIV-infected, as well as describing their quality of life.

The study found that: (1) there is a high prevalence of anxiety and depression in patients with SCADR in this population. (2) Anxiety and depression in patients with SCADR persist for at least six months. (3) Anxiety and depression tend to co-exist in most patients with SCADR (4) SCADR negatively impacts quality of life. (4) SJS/TEN seems to have a more profound and sustained impact on the quality of life than DRESS.

The point prevalence of depression and anxiety symptoms/caseness without borderline depression or anxiety symptoms in our HIV-infected population with SCADR is higher than would be expected in a predominantly HIV-infected population (Marwick and Kaaya, 2010, Martinez et al., 2008). The point prevalence of depression and anxiety in our HIV-infected population with SCADR at six weeks was 46% (22/48) and 42% (20/48) respectively. At 6 months 43% (16/37) exhibited symptoms of depression and 38% (14/37) those of anxiety. This is higher than the 15.8% lifetime prevalence of anxiety and 9.8% prevalence of major depression in the general population of South Africans of all racial groups reported in a study of 4351 adults from 2002 to 2004 where a modified World Health Organization Composite International Diagnostic Interview tool

and the DSM-IV were used to generate diagnoses (Stein et al., 2008). The different populations studied (HIV-infected compared to general population), the time interval (10 years between the two studies), the more discriminatory diagnostic method used in the latter study together with the severity of SCADR could all account for this difference.

Pure anxiety (4%, 2/48), pure depression (8%, 4/48) and comorbid anxiety and depression (38%, 18/48) in our HIV-infected outpatient population with SCADR at six weeks post admission to hospital, is higher than the depression (2.7%, 6/220) and mixed anxiety and depression (12.7%, 28/220) reported in outpatients in Tanzania. We used the HADS tool to identify symptoms/caseness compared to the Tanzanian study that used a validated translated Clinical Interview Schedule-Revised Questionnaire tool to identify symptoms and ICD-10 diagnoses derived from validated threshold scores (Marwick and Kaaya, 2010). Our study was demographically (age, gender and HIV status) comparable with the one in Tanzania. The difference is a reflection of the tool and definitions used. We report symptoms/caseness whereas the Tanzanian study reported diagnoses. This positive diagnostic bias was increased as the HADS tool has a sensitivity of 75%, with a specificity of 81% (Stafford et al., 2007) compared with the Clinical Interview Schedule-Revised tool which is more discriminative with a 100% sensitivity and 96% specificity (Brugha et al., 1999). As a balance, the HADS questionnaire was developed to assess anxiety and depression in medically ill patients and its items are centered on loss of interest and pleasure with somatic features, for example fatigue, insomnia and hypersomnia excluded (Zigmond and Snaith, 1983, WHO, 1993). The combination of visible clinical sequelae, namely dry eyes with associated conjunctivitis, nail dystrophy and persistent skin dyspigmentation in an HIV

setting could contribute to the higher prevalence of anxiety and depression symptoms identified in our study.

Our findings suggest that mental illness is a significant sequel of SCADR. Five of the forty-eight (10%) of patients who reported suicidal ideation at any time following onset of SCADR were referred for psychiatric intervention and treatment when this was identified at 6 weeks post discharge. All of these patients had SJS. None of the patients kept their psychiatry appointment. All five patients received psycho-social intervention as standard of care. No medical treatment was given and one of the patients died from co-morbid disease not suicide. These were SJS patients with co-morbid depression-anxiety that reported suicidal ideation at the two intervals during the study. These findings suggest that SJS/TEN should at best be regarded as a variable risk marker for depression and anxiety comorbidity disorders. A bio-psychosocial approach is needed for optimal management of these patients to prevent mortality.

A meta-analysis of the effects of depression (12 articles) and anxiety (13 articles) on patient adherence with medication concluded that compared with non-depressed patients, the odds of being non-adherent to medication are 3 times greater in depressed patients (DiMatteo et al., 2000). The association between anxiety and noncompliance was variable, small and non-significant. For HIV-infected populations, lifesaving treatments for both HIV and opportunistic infections entail a high pill burden which is itself a risk factor for non-adherence. After SCADR many patients fear recurrences with medication exposure and increases non-adherence. If SCADR patients are depressed, this risk is greatly amplified. The risk of developing drug resistance to anti-retroviral and anti-tuberculosis drugs is directly related to adherence and subsequent increased public

health risk of transmission of resistant strains of disease. Thus, early recognition and treatment of depression in SCADR patients may improve future adherence to treatment regimens.

The higher prevalence of co-morbid anxiety and depression is persistent in SJS/TEN patients 9/13 (69%) for at least six months. Similarly 1/13 (8%) patient with SJS/TEN had persistent depression until the six months of follow-up. In comparison, 1/5 (20%) patient with DRESS had persistent comorbid anxiety and depression. To our knowledge, our study is the first to have found persistent mental disorders in patients with SCADR. Although it is not possible to compare the rates of mental disorders in our study with the published literature, our findings seem to be strong enough to warrant further investigation in larger studies.

The reasons for the higher prevalence of depression and anxiety in patients with SJS/TEN compared to patients with DRESS have not been studied. We hypothesize that SJS/TEN is a much more dramatic disease during the acute stage and is more likely to have a sustained mental impact on the patient than DRESS. Short and long-term sequelae are also more severe in SJS/TEN. On the other hand, patients with DRESS are much more likely to recover completely (Chen et al., 2013, Shiohara et al., 2006, Ghislain and Roujeau, 2002). Further studies are needed to determine factors that predispose patients with SCADR to depression and anxiety.

In this study, we found that depressive and anxiety symptoms co-exist in patients with SCADR. The vast majority of patients, 18/48 (38%) of SCADR with depressive symptoms at six weeks experienced comorbid anxiety symptoms and 13/37 (35%)

patients with SCADR with anxiety symptoms had comorbid depressive symptoms after six months. Importantly, we found 13/18 (72%) had a high HADS score for comorbid anxiety and depression with blistering muco-cutaneous disorders (HADS 15.5) and 5/18 (28%) DRESS (HADS 13.5) at six weeks which 9/13 (69%) persisted for the blistering disorders (HADS 15.5) but 1/5 (20%) DRESS (HADS score 18) at six months follow-up.

The co-existence of anxiety and depression in patients with SCADR at two intervals indicates the severity of SCADR-associated mental conditions and dermatologists and burn unit specialists, who primarily care for these patients, to optimize their treatments to include mental sequelae. Zimmerman et al., reported that the majority of patients with comorbid depression and anxiety expressed a desire to receive treatment for both conditions (Zimmerman et al., 2002). Cognitive Behavior Therapy (CBT), a non-pharmacological intervention, is reported to be effective for treating both depression and anxiety in the general population (Beck, 2005). There is no data on interventions for the simultaneous treatment of depression and anxiety in patients with SCADR. There is no reason to believe that anxiety and depression in patients with SCADR will not respond to standard interventions and CBT would be an ideal intervention as it limits unnecessary exposures to high risk drugs in this vulnerable population. The introduction of CBT as part of standard of care management in patients with SCADR is feasible and recommended.

To our knowledge, this is only the second study in South Africa, to have used a validated DLQI questionnaire to demonstrate and describe the impact of skin disease on patient's quality of life, Our patients' quality of life has similar degree of impairment to that reported among 607 patients attending the general dermatology clinics at GSH in

1999 comprising 52% English-speaking, 35% Afrikaans-speaking and 13% IsiXhosa-speaking patients, low quality of life was found in those affected by dermatitis (DLQI 7) Psoriasis (DLQI 5) atopic dermatitis (DLQI 5) nodular prurigo (DLQI 7.5) papular urticarial (DLQI 7) and urticarial (DLQI 3) using the DLQI translated into each language. Language spoken severity of the skin lesions, unemployment and younger age were independent risk factors for a higher DQLI score. Anxiety and depression were identified as factors needing assessment in quality of life studies. IsiXhosa speakers had the lowest median DLQI scores suggesting isiXhosa speakers were less affected by skin disease compared to Afrikaans and English speakers (Jobanputra and Bachmann, 2000). Our patients taken from the same area but with more dramatic and serious skin disease and comorbidities demonstrated a similar impact on quality of life. The median of all 48 patients DLQI was 4.5 (431/48) at six weeks and 5 (321/37) at six months and confirmed the contribution of anxiety and depression identified in the former study. We were unable to ascertain whether the lower quality of life in our study was related to anxiety, depression, visible symptomatic physical sequelae of SCADR, the severity of the SCADR or other factors. Further studies are needed to identify features of SCADR that are associated with a lower quality of life.

SJS-TEN and TEN significantly impair a patient's overall quality of life (Haber et al., 2005). In our study, TEN (DLQI 14) appeared to have a greater impact on the quality of life compared to SJS (DLQI 3) and DRESS (DLQI 7.5). This pattern was maintained at six months. A possible explanation for the greater impact on quality of life in patients with SJS, SJS-TEN and TEN is that these blistering muco-cutaneous disorders are considered a spectrum of the same disease with TEN being the most severe and life

threatening. The chronic muco-cutaneous sequelae of these blistering disorders are also more severe following TEN (Magina et al., 2003, Oplatek et al., 2006, Sheridan et al., 2002, Yip et al., 2007). The severity and impact on psychosocial functioning and activities of daily living of these often visible sequelae could explain the quality of life effect. Although SJS appeared to have less effect on quality of life (DLQI 3) compared to TEN (DLQI 14), all those with suicide ideation were in this group. SJS-TEN data was too small to determine median DLQI. Larger, formal comparative studies are needed to determine the meaning and significance of these findings.

Patients with blistering SCADR (DLQI 8.4) share a similar impact on the quality of life (DLQI 7.5) as patients affected by DRESS. This is somewhat surprising as DRESS patients although often ill for longer periods do not have as visible muco-cutaneous long-term sequelae compare to SJS, SJS-TEN and TEN. SJS, SJS-TEN and TEN are more dramatic diseases during the acute stage and more likely to have a sustained mental impact on the patient than those with DRESS. Short and long-term sequelae are also more severe and persistent in the blistering SCADRs while patients with DRESS are much more likely to recover completely (Chen et al., 2013, Shiohara et al., 2006, Ghislain and Roujeau, 2002). Intuitively the patients with blistering SCADR would seem more likely to have a greater impact on quality of life. Further studies are necessary to investigate this similarity in quality of life impact.

We were unable to ascertain whether the lower quality of life was related to anxiety, depression, physical sequelae of SCADR or other factors. Further studies are needed to dissect features of SCADR that are associated with a lower quality of life.

Our study has limitations. Firstly, data were collected in only one centre; Groote Schuur Hospital thus limits generalizability of our findings. Hospitalization and HIV infection are associated with anxiety and depression and we could not establish with certainty if these were not confounders in our population. However, the prevalence of anxiety and depression in our study is higher than in published literature. Secondly, a follow-up period of six months is less than ideal; little data is available on the long-term psychological consequences of SCADR. Our data indicate that depression and anxiety stay the same after discharge at 6 months follow up 16/37 (43%) for depression and 14/37 (38%) for anxiety. Haber et al. reported on the late outcomes of SJS-TEN (6) and TEN (7) survivors 38 ± 27 months after discharge from a burns unit. A high level of independent function in activities of daily living was reported but numerous mucocutaneous complications significantly impair overall quality of life (DQLI 9±10). They recommended the need for long-term follow-up of SCADR patients (Haber et al., 2005). Quality of life assessments need longitudinal studies to establish timelines of peak prevalence and their resolution with appropriate management.

Finally, the HADS instrument we chose assesses anxiety and/or depression symptoms/caseness and not anxiety and depression disorders *per-se*, it gives an indications of symptom severity but does not direct management.

As HADS was developed to screen for anxiety and depression in non-psychiatric hospitalized patients and it was thus felt to be an appropriate instrument for our patients with SCADR with significant and severe clinical symptoms. HADS excludes somatic symptoms of illness such fatigue, insomnia or hypersomnia. In contrast alternative tools include somatic symptoms and we chose not to use scales where somatic symptoms

were included as we felt they could lead to an overestimate of anxiety and depression in our ill patients. The validity of the HADS tool was reviewed in 2002 and the authors confirmed that the HADS questionnaire performs well in screening for anxiety and depression separately and for caseness in non-psychiatric patients attending hospital clinics (Bjelland et al. 2002). Despite its brevity, the sensitivity and specificity range for HADS-A and HADS-D using a threshold of 8+ was 0.70 to 0.90, similar to that for longer versions of the General Health Questionnaire. In comparison to other questionnaires in common use for detecting anxiety and depression such as the Beck Depression Inventory, the Spielberger State-Trait Anxiety Inventory, the Clinical Anxiety Scale, the Symptom Checklist 90 scale and the Montgomery Asberg Depression Rating Scale a medium to strong correlation range to HADS of 0.60 to 0.80 was reported. Their conclusion was that the validity of HADS was good to very good and that HADS seems to have at least as good screening properties for identification of anxiety disorders and depression as similar, but more comprehensive instruments.

CHAPTER 5: RECOMMENDATIONS

5.1. RECOMMENDATIONS

1. A qualitative study comparing cases of hospitalized SCADR and a cohort of cases without SCADR in HIV-infected and hospitalized populations during and following discharge from hospital is needed to identify key factors of the phenomenon of living with SCADR which affect the quality of life of patients with SCADR independently of being hospitalized or having HIV infection.
2. Further studies to determine if anxiety and depression impact on treatment compliance in this setting of HIV prevalence. We are planning a prospective follow-up of this cohort to assess adherence to therapy in comparison to those without depression.

5.2. ACKNOWLEDGEMENTS.

The authors acknowledge all the patients participated in this study at the Department of Dermatology, Groote Schuur Hospital, South Africa.

5.3. SOURCES OF FUNDING:

This study was self-funded, with travelling assistance from the Department of Dermatology to the Drug Hypersensitivity Meeting (DHM) and European Academy of Allergy and Clinical Immunology (EAACI), **Bern, Switzerland**, 11 April 2014, for a poster presentation.

5.4. CONFLICT OF INTEREST:

None.

CHAPTER 6: APPENDICES

Appendix 1: Ethical approval: Assessment of the short term and medium term psychological impact

UNIVERSITY OF CAPE TOWN



Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Grootte Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

28 March 2012

HREC REF: 059/2012

Dr E Zitha
Dermatology
G-23
NGSH

Dear Dr Zitha

PROJECT TITLE: ASSESSMENT OF THE SHORT TERM AND MEDIUM TERM PSYCHOLOGICAL IMPACT OF SEVERE CUTANEOUS ADVERSE DRUG REACTION

Thank you for responding to the issues raised by 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 till the 15th April 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please 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



Signed

PROFESSOR M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWAD0001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 312.56 and 312.61.

shuretta

Appendix 2: Annual progress report form

 UNIVERSITY OF CAPE TOWN <small>UNIVERSITEIT VAN KAPSTAD</small>		HUMAN RESEARCH ETHICS COMMITTEE 30 APR 2013		FACULTY OF HEALTH SCIENCES <small>Human Research Ethics Committee</small>	
FHS016: Annual Progress Report / Renewal UNIVERSITY OF CAPE TOWN					
HREC office use only (FWA00001637; IRB00001938)					
This serves as notification of annual approval, including any documentation described below.					
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	15/4/2014		
<input type="checkbox"/> Not approved	See attached comments				
Signature Chairperson of the HREC		Signed		Date Signed	30/4/2013
Principal Investigator to complete the following:					
1. Protocol information					
Date form submitted	15/4/13				
HREC REF Number	059/2012	Current Ethics Approval was granted until	15/4/13		
Protocol title	Assessment of the short term and medium term psychological impact of severe cutaneous adverse drug reaction.				
Protocol number (if applicable)					
Principal Investigator	Dr RJ Lehloonyo				
Department / Office Internal Mail Address	Department for Medicine Dermatology Division				
1.1 Does this protocol receive US Federal funding?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No		
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No		
2. List of documentation					
19 March 2013		Page 1 of 5		FHS016	
<small>(Note: Please complete the Closure form (FHS016) if the study is completed within the approval period.)</small>					

Appendix 3: Prospective cohort study Consent in English

Patient information sheet and Informed Consent for Adults (≥18 years): Assessment of the short-term and medium-term psychological impact of severe cutaneous adverse drug reactions study

You are invited to take part in a research study conducted by Dr Zitha and his team from the University of Cape Town: Department of Medicine, Division of Dermatology. You are invited because you have a severe skin reaction.

In order to decide if you want to take part in this study, you need to understand what is involved. This form gives information about this study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you choose to take part.

Why is this research being done?

The purpose of the study is to find out the psychological and emotional impact on people who have severe skin reactions. It may then be possible to develop ways to help people cope with these feelings.

What will happen if I take part in this study?

You will be asked to complete questionnaires which look at your feelings. For example, the questionnaires will measure if you are feeling depressed or anxious, or embarrassed or self-conscious, and whether the severe skin rash has affected your ability to study or work.

The interview will take place in Ward G23 in the Dermatology Department in Groote Schuur Hospital. It will last about 45 minutes.

What are the risks of taking part in this study?

We do not think the study will harm you in any way. However, some of the questions may upset you. If any of the questions make you feel uncomfortable or you don't want to answer them, you do not have to.

What are the benefits of taking part in this study?

You may not benefit directly from being in the study. However, by volunteering, you may help us understand better how people feel when they have a severe skin reaction. This information will help us to develop ways to help people to deal with their condition.

Will I receive any payment for being in the study?

You will not receive any payment for being in the study. We will compensate you for the costs of coming to the hospital for the study.

What about confidentiality?

The information we collect from this study will be kept confidential. Any information about you will have a number on it instead of your name. Only the

researchers will know what your number is and we will lock that information up or store it on a password-protected computer.

Do I have to take part in this study?

You do not have to take part in this study if you do not wish to do so. Choosing not to take part will not affect your treatment at this hospital. You may also stop taking part in the study at any time. Your care and treatment will not be affected in any way.

Who do I contact about this study?

If you have any questions about the research you may ask us now or later, even after the study has started. If you want to ask questions later, you can contact Professor Todd or Dr Lehloenyha at (021) 404 5269 or (021) 404 5275.

If you have any complaints about the way the research is being done or about your rights and welfare as a research participant, you can contact Professor Marc Blockman who is the Chairperson of the Human Research Ethics Committee in the Faculty of Health Sciences (021) 406 6496.

Consent Statement

I have read this consent form. I have had an opportunity to ask questions and my questions have been answered satisfactorily. I consent willingly to take part in this study. I understand that I can withdraw from the research at any time without in any way affecting my medical care at this hospital. I understand that I will receive a signed copy of this consent form.

Name of participant	Signature
.....
Name of person obtaining consent	Signature
.....

!

Appendix 4: Prospective cohort study Consent in Afrikaans

Pasiënt inligtingsblad en ingeligte toestemming vir Volwassenes (≥18 jaar): Evaluering van die kort termyn en medium termyn sielkundige impak van erge vel ongunstige geneesmiddelreaksies studie

U word uitgenooi om deel te neem aan 'n navorsingstudie wat deur Dr Zitha en sy span van die Universiteit van Kaapstad: Departement Geneeskunde, Afdeling Dermatologie. U word uitgenooi, want jy het 'n ernstige vel reaksie. Ten einde te besluit of jy wil deelneem aan hierdie studie, wat jy nodig het om te verstaan wat betrokke is. Hierdie vorm gee inligting oor die studie, wat saam met jou sal bespreek word. Sodra jy die studie te verstaan, sal jy gevra word om hierdie vorm te onderteken as jy kies om deel te neem.

Hoekom is hierdie navorsing wat gedoen word?

Die doel van die studie is om vas te stel die sielkundige en emosionele impak op mense wat ernstige vel reaksies. Dit kan dan moontlik wees om maniere om mense te help cope met hierdie gevoelens te ontwikkel.

Wat sal gebeur as ek deelneem aan hierdie studie?

Jy sal gevra word om vraelyste wat kyk na jou gevoelens te voltooi. Byvoorbeeld, sal die vraelyste meet as jy depressief of angstig, of skaam of selfbewus voel, en of die ernstige veluitslag geraak jou vermoë om te studeer of werk. Die onderhoud sal plaasvind in Wyk G23 in die Dermatologie Departement in die Groote Schuur-hospitaal. Dit sal duur ongeveer 45 minute.

Wat is die risiko's van deelname aan hierdie studie?

Ons dink nie die studie sal jy skade in enige manier. Maar sommige van die vrae kan jy ontstel. Indien enige van die vrae te maak jou ongemaklik laat voel of jy nie wil hê om dit te beantwoord, het jy nie hoef te.

Wat is die voordele van deelname aan hierdie studie?

Jy mag nie direk baat vind by wat in die studie. Maar deur vrywillige werk, kan jy ons help om beter hoe mense voel wanneer hulle 'n ernstige vel reaksie verstaan. Hierdie inligting sal ons help om maniere om mense te gaan met hul toestand te help ontwikkel.

Ek sal enige betaling vir die feit dat in die studie ontvang?

Jy sal 'n betaling nie ontvang vir die feit dat in die studie. Ons vergoed jou vir die koste van hulle na die hospitaal vir die studie.

Wat van vertroulikheid?

Die inligting wat ons versamel uit hierdie studie sal vertroulik hanteer word. Enige inligting oor u sal 'n aantal het daarop plaas van jou naam. slegs die navorsers sal weet wat jou nommer is en ons sal hierdie inligting op slot of stoor dit op 'n wagwoord-beskermdre rekenaar.

Moet ek om deel te neem aan hierdie studie?

Jy hoef nie deel te neem aan hierdie studie as jy nie wil om dit te doen. Die keuse om nie te deel te neem sal geen invloed op jou behandeling by die hospitaal. Jy kan ook ophou om aan die studie te eniger tyd. Jou sorg en behandeling sal nie geaffekteer word nie op enige manier.

Wie kan ek kontak oor hierdie studie?

Indien u enige vrae oor die navorsing wat jy kan ons nou of later vra, selfs nadat die studie begin het. As jy wil vrae vra later, kan jy kontak Professor Todd of Dr Lehloenya by (021) 404 5269 of (021) 404 5275.

Indien u enige klagtes oor die manier waarop die navorsing gedoen word of oor jou regte en welsyn as 'n navorsingsdeelnemer het, kan jy kontak Professor Marc Blockman wat die voorsitter van die Etiekkomitee Mensnavorsing van die Fakulteit Gesondheidswetenskappe (021) 406 6496.

Toestemming Verklaring

Ek het hierdie toestemmingsvorm gelees. Ek het 'n geleentheid om vrae te vra het en my vrae is bevredigend beantwoord. Ek stem gewillig om deel te neem aan hierdie studie. Ek verstaan dat ek kan onttrek van die navorsing te eniger tyd sonder om enigsins affekteer my mediese sorg by die hospitaal. Ek verstaan dat ek 'n getekende afskrif van hierdie toestemmingsvorm ontvang.

Naam van deelnemer Naam van persoon verkryging van toestemming

!

Handtekening handtekening

Appendix 5: Prospective cohort study Consent in IsiXhosa

Inkcaza zesigulane ngokuzisa uvavanyo kubantu abaneminyaka elishumi nesibhozonagaphezulu uvavanyo olude nlufutshane ngezinto abadibana nazo enagondweni nemfundiso ngamachiza

Uyamenywa ukuba uthathe inxaxheba kuphando lwemfundiso olugulunqwe ngu gqirha Zitha negela lakhe lakhidyunivesithi yase Ntshonakoloni hwicandelo lwezempilo, nakwezolwazi ngolusu lwakho. Umenyiswekuba unenqxakizolusu.

Ukuba uzibone umomngweno nokuthatha inxaxheba koluphando lwenfundiso, kufuneka lwemfundiso, kufuneka ugonde izinto ezibandokanyekayo. Lefomu inika inkcukacha malunga nalemfundo ezakuxoxwa nawe. Ekubbeni wazile ngalemfundiso uzawucelwa ukuba utyikitye lefomu ukuba ukhethat ukabayinxalenye.

Kutheni kufanele lemziwe oluphatha

Isizathu soluphando kukufuna ukuwazi banzi ngokwase ngqondweni nangokwasemphefumleni ngendlela abazivangayo ngolusu lwabo. Kungenzeka kubekhona indlela zokunceda abantu bakwazi ukuziva ngcono ngendlela abaziva ngayo ngolusu lwabo.

Kuzokwengeka ntoni ukuba ndithatha inxaxheba kulemfundiso

Uzawucelwa ukuba uphedule imibuzo ezakujongana nendlela iziva ngayo. Umzekeloimibuzo izobangolwazi ukuba zintoni ezikunika uloyiko, nokungazithembi ingaba ngamaqhakuvha oyikekayo akubangela ukubangela ukuba ungakwazi nokuya emsebenzi or kuyofunnda. Oludliwanondlebe iuyakubanjelwa e G23 kwigumbi lukuxelenga ulusu kwisibhedlela e Groote Schuur izakuthatha imizuzu engamashumi amane anesine.

Zithini incupheko zoku zokuthatha inxaxheba kulemfundiso

Asiqondi ukuba kuzobanochaphazeleko oluyingozi. Kungenzeka eminye imibuzo ikucaphukise, ukuba eminye imibuzo ayikuohathi kakulhle oklanye awufuni kuyiphendula uvumelekile.

Zinto zini ezizofumaneka ekuthatheni inxaxheba kulemfundiso

Unganga fumanitnto koluphando ngaphandle kokba unikeze uncedo. Ungasenza sazi ngokubanzi ukuba abantu bazivanjani xabenengxaki ngolusu lwabo. Ezinkukacna zizakusinceda sifumane indlela zokunceda abantu bakwazi ukumelana nesisimo. Ingaba ndizakuhlulwa na ngokuzibandakanya koluphando?

Awuzofumana ntlawulo ngokubayinxalenye yalemfundiso. Sakubonelela ngendleko zokuza esibhedlela kulemfundiso.

Ulwazi esiluhokolelayo luzakuba sekhushlelweni. Ulwazi esizothi silufumane kuwe luzobane nombolo endaweni yegama lakho. Ngobaphandi bodwa obazoyazi inombolo leyo, olulwazi luzokugcinwa eluvalelweni olu khuselekileyo.

Ithini imfihlelo

Olulwazisiluhokolelayokulemfundiso luzogcinwa elugcinweni oluyimfihlelo. Naluphi ulwazi ngase luzobanenamba endaweni yegama lakho. Ngabaphandi kuphela abazokwazi ukuba ithini namba leyo yakho futhi ulwazi olo luyakugcinwa kwikhomputha enokhuseleko.

Kunyanzelekile ndithathe inxaxheba kulemfundiso

Awunyanzelekanga ukuba uthathe inxaxheba koluphando, ukuba awuziva unako. Kwaye ungayeka naninina ufuna. Unakekelo lwakho nonyango lwakho aluchphazeleki.

Ngubani endinonxebelelana naye ngalemfundiso

Ukuba umemibuzo ngaluphando ungabuza ngoku okanye ngelinye ixesha, nasemva kwemfundiso. Ukuba ufuna ukubuza imbuzo emva kwemfundiso ungatsalela u Professor Todd okanye ugqirha Lehloenya kulomnxeba (021) 406 6496.

Ingxelo mvume

Ndiyifundile lembalelwano. Ndiye ndanalo ithuba lokubuza imibuzo, kwaye imibuzo yam iphedulekile ndoneliseka, ndikulungele ukuthatha inxalenye kulemfundiso. Ndiyaqonda ukuba ndingayeka nanini ndifuna. Lonto ayinakubanalop uncnaphazeleko ekuncedweni kwamkwesibhedlela. Ndiyayiqonda ukuba nadzikuyifumana ikopi etyikityiweyo yale fomu.

Igoma lesigulane..... Igoma lomntu ozofumana.....

Utyikityo.....Utyikityo.....

Appendix 6: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in English

Hospital Anxiety and Depression Scale

~ Scoring Sheet ~

	Yes definitely	Yes sometimes	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

Anxiety 2, 4, 6, 8, 11, 12, 14

Depression 1, 3, 5, 7, 9, 10, 13

Scoring 3, 2, 1, 0 (For items 7 & 10 the scoring is reversed)

GRADING: 0 - 7 = Non-case

8 - 10 = Borderline case

11+ = Case

Appendix 7: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in Afrikaans

Hospitaal Angs en Depressie Skaal

– Telkaart –

	Ja beslis	Ja somtyds	Nee, nie teveel nie	Nee, glad nie
1. Ek wakker vroeg en dan slaap sleg vir die res van die nag.	3	2	1	0
2. Ek kry baie bang of paniekerig gevoelens vir skynbaar geen rede.	3	2	1	0
3. Ek voel ellendig en hartseer.	3	2	1	0
4. Ek voel angstig as ek uit die huis gaan op my eie.	3	2	1	0
5. Ek verloor belangstelling in alles.	3	2	1	0
6. Ek kry hartkloppings of sensasie van vlinders in my maag of my bors.	3	2	1	0
7. Ek het 'n goeie eetlus.	0	1	2	3
8. Ek voel bang of verskrik.	3	2	1	0
9. Ek voel die lewe is nie die moeite werd.	3	2	1	0
10. Ek geniet nog die dinge wat ek altyd doen	0	1	2	3
11. Ek is rusteloos en kan nie still hou nie.	3	2	1	0
12. Ek is meer prikkelbaar as gewoonlik.	3	2	1	0
13. Ek voel asof ek vertraag.	3	2	1	0
14. Kommerwakkende gedagtes voortdurend gaan deur my gedagtes	3	2	1	0

Angs 2, 4, 6, 8, 11, 12, 14

Depressie 1, 3, 5, 7, 9, 10, 13

Telling 3, 2, 1, 0 (Vir items 7 & 10 die telling is omgekeer)

Gradering: 0 – 7 = Geen saak

8 – 10 = Grenslyn saak

11+ = Saak

Appendix 8: Data Collection: The Hospital Anxiety and Depression Scale (HADS)~Scoring Sheet in IsiXhosa

Hospital Anxiety and Depression Scale in Xhosa

- Scoring Sheet -

	Ewe Njalo	Ngamanye amaxesha	Hayi, Hayi kakhulu	Hayi, Hayi kwaphela
1. Ndivuka ngethuba ndilale kakubi ubusuku bonke	3	2	1	0
2. Ndivela ndoyike kokhule okanye ndizole ndingenasi zinzo ngaphandle kwesizathu	3	2	1	0
3. Ndiziva ngingonwabanga yaye ndidanile	3	2	1	0
4. Ndizizwa ndinomsindo xa ndiphuma endlini ndihanma ndendwa	3	2	1	
5. Ndiziva ndingenamdla zwezinye izinto or kwizinto		2	1	
6. Ndiziva ndinexhala okanye ndive ndixuxuzelwa esuswini onkanye esifubeni	3	2	1	0
7. Ndinomdla wokutya	0	1	2	3
8. Ndiziva ndinoloyiko okanye ndisoyika	3	2	1	0
9. Ndiva ingathi ubomi akhukhonto ndiphile yona	3	2	1	0
10. Ndisozonwabela inzito endiziqhelileyo	0	1	2	3
11. Anzikwazi ukuzinza	3	2	1	0
12. Ndiphazamise ka kakhulu kunakuqala	3	2	1	0
13. Ndieiva ingatji ndehlile	3	2	1	0
14. Inqcinga ezinxunguphalisayo zisoko ziengqondweni	3	2	1	0

Anxiety 2,4,6,8,11,12,14

Depression 1 3 5 7 9 10 13 / Scoring 3,2,1,0 for items 7&10 the scoring is reversed.

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

Appendix 9: Data collection Dermatology Life Quality Index (DLQI) in English

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DATE _____ PATIENT NAME _____ SCORE _____

INSTRUCTIONS: The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ✓ one box for each question.

- | | | |
|--|---|---|
| 1. Over the last week, how itchy, sore, painful or stinging has your skin been? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Not relevant |
| 2. Over the last week, how embarrassed or self conscious have you been because of your skin? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all | <input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all |
| 3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 4. Over the last week, how much has your skin influenced the clothes you wear? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 5. Over the last week, how much has your skin affected any social or leisure activities? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 6. Over the last week, how much has your skin made it difficult for you to do any sport? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 7. Over the last week, has your skin prevented you from working or studying?

If "No", over the last week how much has your skin been a problem at work or studying? | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Not relevant | <input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all |
| 8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 9. Over the last week, how much has your skin caused any sexual difficulties? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |
| 10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant | <input type="checkbox"/> Very much
<input type="checkbox"/> A lot
<input type="checkbox"/> A little
<input type="checkbox"/> Not at all
<input type="checkbox"/> Not relevant |

Please check you have answered EVERY question. Thank you.

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Appendix 10: Data collection Dermatology Life Quality Index (DLQI) in Afrikaans

LEWENSAGEHALTE VAN PASIENT MET VEL KWALE

DLQI

Hospital No:

Datum:

Score:

Name:

Diagnose:

Address:

Die doel van hierdie vraelys is om te bepaal tot watter mate jou vel probleem jou lewe in die **AFGELOPE WEEK** geaffekteer het. Merk asseblief een blokkie per vraag.

1	Hoe jeukerig, seer of branderig was jou vel die afgelope week?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2	Hoe selfbewus of skaam het hy die afgelope week gevoel as gevolg van jou vel?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3	Gedurende die afgelope week, tot watter mate het jou vel jou benadeel om inkopies te gaan doen, huis op te pas of tuinwerk te doen?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
4	Gedurende die afgelope week, tot watter mate het jou vel die klere wat jy dra beïnvloed?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
5	Gedurende die afgelope week, hoe baie het jou vel jou sosiale of ontspannings aktiwiteite geaffekteer?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
6	Gedurende die afgelope week, tot watter mate het jou vel dit vir jou moeilik gemaak om aan sport deel te neem?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
7	Gedurende die afgelope week, het jou vel jou verhoed om te werk of studeer ?	Ja Nee	<input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
	Indien "Nee", tot watter mate was jou vel 'n probleem gedurende werk of studies , die afgelope week?	Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
8	Tot watter mate het jou vel probleme veroorsaak met jou gesel , of enige van jou vriende of familieledede , die afgelope week?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
9	Gedurende die afgelope week, het jou vel enige seksuele probleme veroorsaak?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>
1	Gedurende die afgelope week, tot watter mate was die behandeling vir jou vel 'n probleem, byvoorbeeld, dat die jou huis bemors, of jou tyd opneem?	Vreeslik baie Baie Min Glad nie	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Nie van toepassing <input type="checkbox"/>

Maak asseblief seker dat ELKE vraag beantwoord is. Dankie.

Appendix 11: Data collection Dermatology Life Quality Index (DLQI) in IsiXhosa

UBOMI OBUPHILWA NGABANTU ABANEZIFO ZESIKHUMBA

DLQI

Hospital No:

Umhla:

Score:

Name:

Diagnosis:

Address:

Sicele uphendule lemibuzo ilandelayo, malunga nendlela isifo sakho sesikhumba esiyitshintshe ngayo indlela obuphila ngayo KULEVEKI EPHELILEYO. Bhale umkrwelo kwibhokisi enye yombuzo ngamnye.

1.	Kuleveki ephelileyo, isikhumba sakho sirhawuzele, siqaqambe, sibebuhlungu okanye sihlabe kangakanani?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2.	Kuleveki ephelileyo, ubenentloni okanye akwakwazi ukuzithemba kangakanani ngenxa yesikhumba sakho?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3.	Kuleveki ephelileyo isikhumba sakho siphazamisene kangakanani nokuphuma kwakho uye evenkileni okanye usebenze endlwini okanye egadini yakho?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
4.	Kuleveki ephelileyo, isikhumba sakho sibe nefuthe kangakanani nempahla oyinxibayo?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
5.	Kuleveki ephelileyo ingaba isifo sesikhumba siyiphazamise kangakanani na impilo yakho yasekuhlaleni okanye eyolonwabo?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
6.	Kuleveki ephelileyo isikhumba sakho senze kwanzima kangakanani ukuba udlale nawuphi na kwezemidlalo?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
7.	Kuleveki ephelileyo, ingaba isikhumba sakho sikwenze akwakwazi ukusebenza okanye ukufunda na?	Ewe Hayi	<input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
	Ukuba impendulo ngu "hayi", kuleveki ephelileyo, isikhumba sakho sibeyingxaki engakanani emsebenzini okanye ekufundeni?	Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
8.	Kuleveki ephelileyo, isikhumba sakho senze iingxaki ezingakanani na neqabane lakho, abahlobo okanye izalamane zakho?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
9.	Kuleveki ephelileyo ingaba isikhumba sakho sikwenzele iingxaki ezingakanani na xa ubusabelana ngesondo nesithandwa sakho (kukuthi oko xa ulele nowakwakho)?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>
10.	Kuleveki ephelileyo ibengakanani ingxaki yempatho yesikhumba, umzekelo ukwenza ikhaya mdaka okanye ukuthabatha ixesha lakho?	Kakhulu gqitha Kakhulu Kancinci Bekungeko ngxaki mpela	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Awunxumelelananga nam lombuzo <input type="checkbox"/>

Appendix 12: The raw data for each patient

No.	Sex	Age	Race	HIV	CD4 count	SCADR	Drug	Co-morbid disease	HADS-A 6 weeks	HADS-D 6 weeks	HADS 6 weeks	DLQI score 6 weeks	Suicide ideation treatment	HADS-A 6 months	HADS-D 6 months	HADS 6 months	DLQI score 6 months
1	F	25	Black African	+ve	262	SJS	NVP		Case (A ⁺) 13	Normal (D ⁻) 3	16	Extreme 19	No	Normal (A ⁻) 6	Normal (D ⁻) 6	12	Extreme 22
2	F	35	Black African	+ve	401	SJS	NVP		Case (A ⁺) 11	Normal (D ⁻) 7	18	Nil 1	No	Deceased	Deceased	Deceased	Deceased
3	F	31	Black African	+ve	92	SJS	NVP		Case (A ⁺) 15	Case (D ⁺) 12	27	Nil 0	No	Normal (A ⁻) 2	Borderline (D ⁰) 8	10	Nil 0
4	F	38	Black African	+ve	149	SJS	INH	PTB	Borderline (A ⁰) 8	Case (D ⁺) 11	19	Large 16	No	Borderline (A ⁰) 8	Case (D ⁺) 11	19	Nil 0
5	F	34	Black African	+ve	299	SJS	NVP		Case (A ⁺) 17	Case (D ⁻) 15	32	Extreme 27	No	Case (A ⁻) 21	Case (D ⁺) 16	37	Extreme 23
6	F	29	Black African	+ve	228	SJS	NVP		Normal (A ⁻) 0	Case (D ⁻) 11	11	Nil 0	No	Relocated	Relocated	Relocated	Relocated
7	F	30	Black African	+ve	545	SJS	NVP		Normal (A ⁻) 6	Normal (D ⁻) 2	8	Small 3	Yes LTFU	Borderline (A ⁰) 9	Borderline (D ⁰) 10	19	Large 17
8	F	37	Black African	+ve	209	SJS	NVP		Case (A ⁺) 11	Case (D ⁺) 14	25	Large 12	Yes LTFU	Case (A ⁺) 14	Case (D ⁺) 17	31	Large 17

9	F	35	Black African	+ve	170	SJS	NVP		Borderline (A ⁰) 8	Normal (D ⁻¹) 4	12	Moderate 6	No	Case (A ⁺¹) 13	Borderline (D ⁰) 10	23	ND
10	F	25	Black African	+ve	257	SJS	NVP		Normal (A ⁻¹) 0	Normal (D ⁻¹) 3	3	Small 2	No	Normal (A ⁻¹) 0	Normal (D ⁻¹) 0	0	Nil 0
11	F	26	Mix race	+ve	630	SJS	EFV		Normal (A ⁻¹) 5	Normal (D ⁻¹) 6	11	Nil 1	Yes LTFU	Case (A ⁺¹) 18	Case (D ⁺¹) 17	35	ND
12	F	35	Mix race	+ve	205	SJS	LTG		Borderline (A ⁰) 10	Normal (D ⁻¹) 6	16	Small 3	No	Relocated	Relocated	Relocated	Relocated
13	F	28	Mix race	+ve	-	SJS	NVP	Gout & PTB	Normal (A ⁻¹) 3	Normal (D ⁻¹) 4	7	Small 2	Yes LTFU	Deceased	Deceased	Deceased	Deceased
14	F	77	Mix race	-ve	-	SJS	ALLO	Epilepsy	Case (A ⁺¹) 17	Case (D ⁺¹) 18	35	Nil 0	No	Normal (A ⁻¹) 7	Case (D ⁺¹) 11	18	Nil 0
15	M	77	Black African	-ve	-	SJS	PHE		Normal (A ⁻¹) 4	Normal (D ⁻¹) 6	10	Small 4	No	Relocated	Relocated	Relocated	Relocated
16	F	31	Black African	+ve	1213	SJS	NVP		Normal (A ⁻¹) 4	Normal (D ⁻¹) 4	8	Nil 0	No	Normal (A ⁻¹) 3	Normal (D ⁻¹) 2	5	Nil 0
17	M	20	Black African	+ve	-	SJS	Unk		Normal (A ⁻¹) 3	Normal (D ⁻¹) 4	7	ND	No	Relocated	Relocated	Relocated	Relocated
18	F	62	Black African	-ve	-	SJS	Unk		Normal (A ⁻¹) 3	Normal (D ⁻¹) 5	8	Small 5	No	Normal (A ⁻¹) 2	Borderline (D ⁰) 9	11	Nil 0
19	F	31	Mix race	+ve	267	SJS	Unk	Epilepsy	Case (A ⁺¹) 18	Case (D ⁺¹) 20	38	Small 3	No	Deceased	Deceased	Deceased	Deceased

20	F	23	Black African	+ve	724	SJS	Unk	PTB	Normal (A ⁺¹) 7	Borderline (D ⁰) 9	16	Nil 0	No	Normal (A ⁺¹) 3	Borderline (D ⁰) 10	13	Nil 0
21	F	52	Mix race	-ve	-	SJS	ALLO	PTB	Case (A ⁺¹) 11	Case (D ⁺¹) 14	25	Extreme 22	No	Case (A ⁺¹) 11	Case (D ⁺¹) 12	23	Moderate 6
22	F	33	Black African	+ve	89	SJS	NVP		Case (A ⁺¹) 18	Case (D ⁺¹) 17	35	Large 17	No	Case (A ⁺¹) 19	Case (D ⁺¹) 11	30	Large 15
23	F	35	Black African	+ve	-	SJS	NVP		Case (A ⁺¹) 20	Case (D ⁺¹) 17	37	Extreme 26	Yes LTFU	Case (A ⁺¹) 18	Case (D ⁺¹) 13	31	Extreme 29
24	F	23	Black African	+ve	97	TEN	ALLO		Normal (A ⁺¹) 5	Normal (D ⁺¹) 6	11	Small 5	No	Normal (A ⁺¹) 4	Borderline (D ⁺¹) 8	12	Large 12
25	M	35	Black African	-ve	280	TEN	NVP		Case (A ⁺¹) 17	Case (D ⁺¹) 14	31	Large 20	No	Case (A ⁺¹) 14	Case (D ⁰) 11	25	Extreme 23
26	F	35	Black African	+ve	291	TEN	CTX		Normal (A ⁺¹) 6	Borderline (D ⁻¹) 8	14	Large 13	No	Borderline (A ⁺¹) 8	Borderline (D ⁰) 9	17	Large 14
27	F	25	Black African	+ve	345	TEN	NVP		Normal (A ⁺¹) 4	Normal (D ⁺¹) 6	10	Large 15	No	Normal (A ⁺¹) 3	Borderline (D ⁺¹) 9	12	Small 4
28	F	37	Black African	+ve	422	TEN	Rif		Case (A ⁺¹) 16	Case (D ⁰) 12	28	Nil 1	No	Case (A ⁰) 16	Case (D ⁰) 12	28	Large 11
29	M	48	Mix race	-ve	-	TEN	NVP		Normal (A ⁺¹) 3	Normal (D ⁻¹) 7	10	Small 3	No	Normal (A ⁺¹) 4	Borderline (D ⁰) 8	12	Nil 0
30	M	49	Black African	+ve	126	TEN	INH		Case (A ⁺¹) 17	Case (D ⁻¹) 18	35	Extreme 26	No	Case (A ⁺¹) 17	Case (D ⁺¹) 14	31	Extreme 27

31	M	24	Black African	-ve	135	TEN	PHE		Case (A+) 12	Case (D+) 12	24	Large 17	No	Deceased	Deceased	Deceased	
32	F	34	Black African	+ve	114	SJS-TEN	BAN		Case (A+) 15	Case (D+) 11	26	Extreme 21	No	Case (A+) 13	Case (D+) 14	27	Extreme 23
33	M	46	Black African	+ve	700	SJS-TEN	NVP		Borderline (A ⁰) 10	Normal (D-) 7	17	Small 5	No	Case (A+) 12	Case (D+) 11	23	Moderate 8
34	F	36	Black African	+ve	552	SJS-TEN	NVP		Normal (A+) 0	Normal (D-) 2	2	Nil 1	No	Normal (A+) 2	Normal (D+) 1	3	Nil 0
35	F	27	Black African	+ve	887	DRESS	EFV		Normal (A+) 2	Normal (D-) 3	5	Nil 0	No	Borderline (A ⁰) 9	Normal (D-) 6	15	Small 5
36	M	33	Black African	-ve	329	DRESS	Rif		Case (A+) 21	Case (D+) 15	36	Extreme 31	No	Borderline (A ⁰) 9	Case (D+) 15	24	Extreme 30
37	M	22	Mix race	-ve	-	DRESS	Rif		Case (A+) 11	Case (D+) 13	24	Large 17	No	Normal (A+) 2	Normal (D-) 2	4	Small 2
38	M	36	Mix race	+ve	235	DRESS	BAN		Normal (A+) 6	Case (D+) 14	20	Large 17	No	Normal (A+) 0	Normal (D-) 0	0	Nil 0
39	F	47	Black African	+ve	275	DRESS	Rif		Normal (A+) 0	Normal (D-) 2	2	Nil 0	No	Normal (A+) 0	Normal (D-) 0	0	Nil 0
40	F	37	Black African	+ve	247	DRESS	NVP		Normal (A+) 6	Normal (D-) 6	12	Large 11	No	Normal (A+) 4	Normal (D-) 0	4	Small 5

41	F	40	Black African	+ve	-	DRESS	NVP		Normal (A ⁺) 0	Normal (D ⁺) 0	0	Nil 0	No	Normal (A ⁻) 0	Normal (D ⁻) 0	0	Nil 0
42	F	29	Mix race	+ve	198	DRESS	NVP		Case (A ⁺) 15	Case (D ⁺) 12	27	Nil 1	No	Normal (A ⁻) 6	Normal (D ⁻) 6	12	Moderate 6
43	M	46	Black African	+ve	135	DRESS	EFV		Case (A ⁺) 17	Case (D ⁺) 19	36	Small 3	No	Case (A ⁻) 17	Case (D ⁻) 13	30	Small 5
44	F	27	Black African	+ve	100	DRESS	NVP		Borderline (A ⁰) 10	Case (D ⁺) 14	24	Large 26	No	Case (A ⁻) 11	Case (D ⁻) 15	26	Large 17
45	F	24	Black African	+ve	-	DRESS	PHE		Case (A ⁺) 14	Case (D ⁺) 13	27	Large 14	No	Relocated	Relocated	Relocated	Relocated
46	F	44	Black African	+ve	120	DRESS	EFV		Normal (A ⁻) 5	Normal (D ⁻) 0	5	Large 11	No	Normal (A ⁻) 1	Normal (D ⁻) 3	4	Nil 0
47	M	43	Black African	-ve	-	DRESS	INH		Normal (A ⁻) 3	Normal (D ⁻) 3	6	Small 4	No	Relocated	Relocated	Relocated	Relocated
48	M	55	Black African	+ve	30	DRESS	Rif		Normal (A ⁻) 0	Normal (D ⁻) 3	3	Nil 0	No	Relocated	Relocated	Relocated	Relocated

aHIV = human immunodeficiency virus, DRESS = A drug reaction with eosinophilia and systemic symptoms, SJS = Steve-Johnson syndrome, SJS-TEN overlap = Steve-Johnson syndrome and toxic epidermal necrolysis overlap, TEN = Toxic epidermal necrolysis. HADS-A = Hospital Anxiety and Depression Scale-Anxiety, HADS-D = Hospital Anxiety and Depression Scale-Depression, DLQI = The Dermatology Life Quality Index.

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