Assessment of lymphadenopathy in patients with drug reaction and eosinophilia (DRESS): a comparative, descriptive study

By

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DECLARATION

I, **Musonda Sharon Machona**, declare that this dissertation is based on my original work, (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. Neither has this work been reported or published prior to registration for the abovementioned degree. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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This thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software), and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

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DEDICATION

I dedicate this work to:

My parents - my late father Paul Eric Machona and my mother Beatrice Machona; for raising me up to understand that education can never be taken away from you. Without their constant love and support none of my achievements would be possible. My husband - Paul Mambwe Chilwesa; for helping me see that no dream is too big to imagine into reality and being a source of inspiration and strength. My children – Fayanna and Elijah; for being patient enough to allow me to be away from them for many hours on end to complete this project. My siblings - Sylvia, Penelope, Paul and Katie; my sounding boards that let me know how far I can reach and assure me that nothing is impossible.

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FORMAT

This thesis has been submitted in the **Published paper format** and has been published in the Journal of Allergy and Clinical Immunology: Global (JACI-Global) with me, Musonda Sharon Machona, as first author with the title: "Advanced Human Immunodeficiency virus (HIV) does not impact the ability to utilize lymphadenopathy in the assessment of DRESS syndrome in HIV and tuberculosis. A prospective comparative study."

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The format of the manuscript is in keeping with the author guidelines as stipulated by JACI – In practice (available at https://www.jaci-global.org/content/authorinfo and in appendices below).

CONTRIBUTIONS

The data from this study was collected from the IMARI-SA registry and biorepository (UCT HREC R031/2018).

In addition to myself, Musonda Sharon Machona as the first author, the manuscript was co-authored by Rudzani Muloiwa, Mireille Porter; and Rannakoe Lehloenya and Jonathan Peter as Supervisors (Division of Dermatology and Allergology and Immunology respectively).

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ABBREVIATIONS

DRESS	drug reaction with eosinophilia and systemic symptoms
ART	antiretroviral therapy
HIV	human immunodeficiency virus
TB	tuberculosis
RegiSCAR	international registry of severe cutaneous adverse reactions
CADRs	cutaneous adverse drug reactions
HHV-6	human Herpes virus 6
DIHS	drug-induced hypersensitivity syndrome
SIV	simian immunodeficiency virus

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ABSTRACT

Advanced HIV does not impact the ability to utilize lymphadenopathy in the assessment of DRESS syndrome in HIV and tuberculosis. A prospective comparative study.

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ABSTRACT (252 words)

Background: RegiSCAR validation criteria for DRESS includes lymphadenopathy, a frequent feature of both tuberculosis (TB) and HIV. TB is the most common HIV-associated co-infection. Advanced HIV is associated with lymph node (LN) fibrosis. It is not clear if this negatively impacts case validation in HIV-associated DRESS. To answer this question, we designed a prospective descriptive study to assess lymphadenopathy in various co-morbid HIV/TB/DRESS combinations.

Objectives: To describe the prevalence of DRESS-associated lymphadenopathy and characterize LN quality, size, and distribution in a high HIV/TB burden setting over time.

Methods: We prospectively and systematically examined LN in 25 consecutive acute DRESS cases hospitalized at a South African tertiary centre and 10 hospitalised non-DRESS HIV/TB co-infected controls.

Results: 14/25 cases (56%) were HIV-infected, with a median (IQR) CD4 count of 254(66-478) cells/mm^3 and 7/14 were TB co-infected. Using RegiSCAR criteria, 12/25(46%) were definite, 8/25(31%) probable and 5/25(23%) possible DRESS cases. Possible cases were excluded in the analysis. 15/20(75%) had LN in ≥2 anatomical sites, including 7/7(100%) with HIV/TB co-infection. In contrast, 1/5(20%) hospitalised non-DRESS HIV/TB co-infected controls had LN. Cervical LN in 15/17(88%) was commonest, followed by axillary (76%) and inguinal (59%) respectively. Cervical LN ranged between 1- 2cm in size. Amongst the 8/20(40%) that followed up, LN had regressed in all within 6 weeks of stopping the offending drug and initiation of TB treatment. There was no correlation with CD4 cell count and LN.

Conclusion: Lymphadenopathy is a common feature of acute DRESS even amongst HIV and TB-co-infected patients with advanced immunosuppression.

Capsule Summary (71 words)

Lymphadenopathy is one of the diagnostic criteria for DRESS, a relatively common drug reaction in HIV-infected persons. HIV has been reported to predispose to lymph node fibrosis, potentially impacting clinical lymph node responses. This study suggests that HIV infection, advanced disease included, does not impact on DRESS-associated lymph node responses which needs further research to verify. It supports continuing inclusion of lymphadenopathy as a feature of DRESS, even in HIV-infected persons.

Key words: lymphadenopathy; HIV; tuberculosis; DRESS syndrome; RegiSCAR diagnostic criteria.

Abbreviations used:

DRESS – drug reaction with eosinophilia and systemic symptoms

HIV – human immunodeficiency virus

IQR – interquartile range

TB – tuberculosis

LN – lymph node

RegiSCAR – Registry of Severe Cutaneous Adverse Reaction

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon, potentially life-threatening, idiosyncratic reaction to a drug that is characterized by a rash with systemic features. It can arise anywhere between two and eight weeks after drug initiation.[1] DRESS presents as a morbilliform eruption associated with fever, lymphadenopathy, haematologic abnormalities and can affect multiple internal organs.[2] Lymphadenopathy, defined as lymph nodes that are abnormal in size and consistency, is common in DRESS syndrome and is seen in approximately 75% of cases. [3, 4] A focal or generalized presentation of lymphadenopathy is associated with DRESS syndrome, with a predilection to cervical, axillary, and inguinal nodes and the affected nodes may be tender.[5, 6] Criteria for case definition have been proposed by the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) study group and the Japanese Research Committee on Severe Cutaneous Adverse Reaction. Lymphadenopathy in at least two sites is included in both diagnostic criteria. [7, 8]

The RegiSCAR group has developed a diagnostic validation score, combining clinical and biological criteria for validation of potential DRESS cases. The score assigns each of the eight major features a score ranging from -1 to 2 points for a maximum score of 9 points. The certainty of diagnosis is based on the total score: <2 points: no case; 2–3 points: possible case; 4–5 points: probable case; >5 points: definite case **(Annexure 1)**.[7, 9, 10] In the score lymphadenopathy carries 1 point, if absent 0 points. A single point has the potential to impact the certainty of the diagnosis of DRESS. Lymphadenopathy together with eosinophilia, fever, and liver injury have been significantly associated with a “probable” or “definite” case of DRESS. [11]

During the latent phase of human immunodeficiency virus (HIV) infection, there is continuous depletion of lymphocytes and progressive involution of the germinal centres of lymph nodes.

Over time, the nodes become smaller or impalpable.[12, 13] TB lymphadenopathy contributes up to 43% of peripheral lymph nodes in TB endemic settings, frequently presenting as chronic and non-tender lymphadenopathy.[14]Cervical lymphadenopathy is a common presentation of extrapulmonary TB, reported in 63-77% of cases in contemporary series.[15-17]It has been suggested that the non- resolving adaptive responses in HIV result in collagen deposition and fibrosis of lymph nodes.[18-21] However, it is not clear if this impacts the detection of lymphadenopathy in HIV- associated DRESS. To answer this question, we decided to perform a prospective case-control study evaluating lymphadenopathy in HIV infected and uninfected patients with DRESS.

Objectives: To describe the prevalence of DRESS-associated lymphadenopathy and characterize LN quality, size and distribution in a high HIV-TB burden setting over time.

METHODS

Inclusion criteria:

1. All participants who fulfilled the RegiSCAR criteria for “definite” or “probable” DRESS regardless of age.
2. Participants who were willing and able to sign informed consent. In the case of minors, informed consent was sort from parents or legal guardians.
3. Control group – Participants that were HIV and TB-coinfected but did not have DRESS syndrome

Exclusion criteria:

Participants who were unwilling to sign an informed consent.

Study setting and design

In a single-blinded, case-control study conducted between September 2018 and November 2020, 25 consecutive patients hospitalized for suspected acute DRESS and 10 hospitalized controls without DRESS were enrolled. All the controls were HIV-infected, five TB-coinfected and five TB uninfected. Within 48 hours of admission, both the cases and controls were clinically and systematically examined for lymphadenopathy based on **Figure 1** by two independent clinicians blinded to their HIV status to a consensus.[22] For this study, lymph nodes >1 cm diameter were considered clinically relevant, except for the epitrochlear,

supraclavicular, popliteal and iliac nodes where the cut-off was 0.5 cm.[23, 24] Apart from presence and anatomical location, their size, character and tenderness were catalogued. Disagreements were settled by a senior clinician as the third reviewer. Six weeks post hospital discharge, all the cases were recalled and the lymph node examinations repeated as before. Using clinical photographs, histopathology, clinical and laboratory data, all the cases clinically diagnosed as DRESS were categorised as definite, probable, possible or no case, using the validated diagnostic validation score developed by the RegiSCAR group .[10] (**Annexure 1**) Only the cases validated as definite and probable were included in the analysis, The study was conducted at Groote Schuur Hospital, a tertiary hospital in Cape Town, South Africa and approved by the Human Research Ethics Committee of the University of Cape Town. All participants provided written informed consent.

RESULTS

The demographic and clinical characteristics of all the 25 suspected DRESS cases are summarised in **Table 1.** The median age was 38 years (IQR 27-44) and were majority female (64%). Twenty cases met the criteria for probable or definite DRESS and were included in the analysis. Thirteen of the 20 (65%) were HIV infected. Seven of those with HIV (54%) had advanced disease and seven (54%) were co-infected with TB. Three of those with HIV TB co-infection (43%) had pulmonary TB while the other four had disseminated disease. Fifteen of the 20 (75%) had lymphadenopathy in more than one site. All the cases that were HIV-infected had lymphadenopathy in at least one site and 12/13 (93%) in at least two. HIV and TB co-infection (n=7) guaranteed lymphadenopathy in at least two sites. This dropped to 43% (n=7) in the HIV-uninfected. All three cases (15%) without lymphadenopathy in the analysis were HIV uninfected. **Table 2**

Amongst the 17 cases with lymphadenopathy in at least one site, cervical nodes were the most affected (88%), followed by axillary (76%) and inguinal (59%). Amongst the 15 with lymphadenopathy in at least 2 sites cervical and axillary nodes were found equally in 13/15 (87%). All seven cases with HIV/TB coinfection had lymphadenopathy in at least 2 sites, with all having axillary nodes and 6/7 cervical. Inguinal nodes were found in three cases, one with pulmonary and two with extrapulmonary TB. The majority of lymph nodes (60%), regardless of HIV status, were firm and rubbery. None of the cases had stony hard lymph nodes. The lymph nodes mostly ranged between 1-2 cm. **Tables 2 and 3**

Five of the 10 controls were co-infected with HIV and TB while the other five were only HIV-infected without TB. The demographic features of the controls are shown in **Table 4.** Two of the ten (20%) controls had lymphadenopathy in two or more sites, one each with TB and without active TB. The size and consistency of the lymph nodes was similar to the cases. **Table 5 and Supplementary table 2**

DISCUSSION

To the best of our knowledge, this is the first study to investigate the prevalence of lymphadenopathy in HIV-infected versus uninfected DRESS cases, with or without TB, two common co-infections and both strongly associated with lymphadenopathy. Contrary to our hypothesis, we found that being HIV infected and having TB were additional risk factors for lymphadenopathy amongst DRESS cases, refuting the suggestion that lymphadenopathy is less prevalent in HIV infection. Based on our own experience and reports in the literature that fibrosis is a major feature in lymph nodes infected with HIV,[18-21] we had hypothesised that DRESS cases with advanced HIV would be less likely to have lymphadenopathy. Ninety-three percent of the DRESS cases infected with HIV had lymphadenopathy and met the threshold (≥2 sites) to add a point to the RegiSCAR validation score. Furthermore, amongst the DRESS cases without HIV or TB, 57% had single site lymphadenopathy, while 43% had it recorded in at least 2 sites, further supporting lymphadenopathy as a feature of DRESS independent of an additional infective cause. One of the five (20%) HIV/TB co-infected controls had lymphadenopathy in two or more sites. Similarly, only 1/5 (20%) HIV-infected with no TB had lymphadenopathy in two or more sites, highlighting that HIV and TB do not always cause lymphadenopathy. However, it is not clear if the reported fibrosis of lymph nodes in HIV impacts on their size, clinical characteristics and functionality.

Amongst those infected with HIV, lymphadenopathy was recorded across the CD4 count values which ranged from 5-916 cells/uL.. Unfortunately, viral loads, likely a better marker of HIV viral replication and ongoing immune dysregulation was not available for a significant number of the cases. Only 8 HIV infected cases had a record of Viral load done. The Viral loads of 4 participants ranged from 40 to 6989 copies with the other 4 participants having undetectable Viral Loads. All of the 8 cases with these results available presented with lymphadenopathy. Regardless of whether the Viral load was detectable or not, suggesting that Viral load does not play a significant role in the development of lymphadenopathy.

When considering all 3 (DRESS, HIV and TB co-infection) 10/15 had both cervical and axillary involvement, with 8 having inguinal nodes. In comparison to cases with DRESS and HIV but no TB, 4/15 had cervical involvement, 3/15 had axillary involvement and 5/15 had inguinal involvement. In the DRESS only (no HIV or TB infection) subgroup, 3/15 had both cervical and axillary involvement with only 2 with inguinal nodes. This suggests that in DRESS the affected

nodes are more generalised. The lymph nodes were mostly 1 - 2cm with firm and rubbery consistency. The inability to detect lymph nodes <1 cm in this study supports published reports that the threshold for consistent palpability of lymph nodes by experienced clinicians is 1.5 cm.[23]

Amongst the definite and probable DRESS cases, we found 75% to have lymphadenopathy that met the RegiSCAR criteria. This compares well, even with the upper margins of previous studies that assessed lymphadenopathy in DRESS. A prospective RegiSCAR study of 117 probable or definite DRESS cases revealed lymphadenopathy in two or more sites in 54%.[7] A review of 130 probable and definite paediatric DRESS cases found 75% to have lymphadenopathy.[25] A Japanese study investigating the association of HHV-6 reactivation with flares and severity of DRESS in 100 cases demonstrated that 71% of patients who had an increase in HHV-6 IgG titres had lymphadenopathy, while only 26% of those with no increase in HHV-6 IgG titres had lymphadenopathy.[26]

Eight cases (40%) were available for follow-up at 6 weeks, six of them HIV-infected and four with HIV/TB coinfection. Lymphadenopathy had resolved in all of them. The high drop-out in the study was due to two in-hospital deaths and disruptions by the COVID-19 pandemic. This further supports the reactive ability of lymph nodes in advanced HIV. However, the quality of this response in DRESS is not clear and needs further investigation.

The major limitation of this study is a high loss to follow-up due to COVID-19 pandemic. The other limitations were a small sample size due to the relative rarity of DRESS and paucity of paediatric cases. The only participant under the age of 18 years was 15 years old. The viral load, a marker for ongoing viral replication was known in a small proportion of HIV-infected cases.

CONCLUSIONS

Contrary to our hypothesis, we found that being HIV infected and having TB were additional risk factors for lymphadenopathy amongst DRESS cases. Our study supported lymphadenopathy as an independent feature of DRESS. We found CD4 count, which we used as a proxy for WHO stage of HIV, not to correlate of presence and quality of lymphadenopathy. Axillary, cervical and inguinal nodes formed the majority of affected nodes in DRESS. Lastly, we established that DRESS-associated lymphadenopathy, even in the presence of treated TB and HIV resolves with eliminating the offending drug and initiating TB treatment.

RECOMMENDATIONS

It is our recommendation that a follow up, larger sample sized study is done to further reduce the bias and solidify conclusions. Medications as well as time frames of commensal that would be identified as triggers of DRESS would need to be recorded especially anti TB/antiretroviral drugs as a result of clinical resemblance to Immune Reconstitution Inflammatory Syndrome (IRIS). It would be best to include a longer follow up period as this would also help to differentiate between the two conditions after reinitiation of antiretroviral therapy and antiTB medication.

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CONFLICTS OF INTEREST

None

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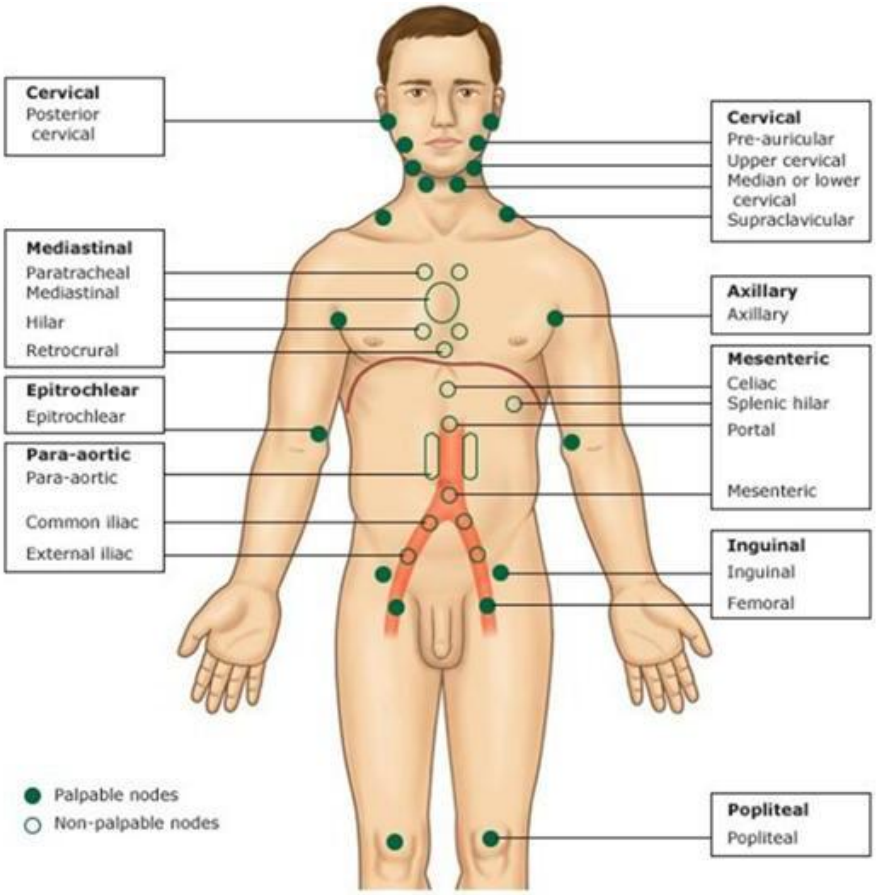
Figure 1 : Palpable and non-palpable lymph nodes



Source [22]

Table 1: Demographics and clinical characteristics of the cases diagnosed with possible, probable or definite DRESS (n=25)

Variables	All (n=25)
Age in years, median (IQR)	38 (27-44.5)
Gender	
Male, n (%)	9 (36)
Female, n (%)	16 (64)
HIV status	
HIV infected, n (%)	14/25 (56)
WHO clinical stage 3 and 4, n (%)	7/14 (50)
Median CD4 cell count (IQR)	253.5 (66-478)
HIV viral load	
Not done n (%)	6/14 (43)
Undetectable n (%)	4/8 (50)
Median (range) copies/ml	950 (40-6989)
HIV uninfected, n (%)	11/25 (44)
TB, n (%)	7/14 (50)
Pulmonary TB, n (%)	3/7 (43)
Disseminated TB, n (%)	4/7 (57)
Co-morbidities	
Hypertension, n (%)	1/25 (4)
Hepatitis B infection, n (%)	1/25 (4)
Epilepsy, n (%)	1/25 (4)
Asthma, n (%)	1/25 (4)
Gout, n (%)	1/25 (4)

Abbreviations: IQR – interquartile range; **HIV** – Human Immunodeficiency virus; **WHO** – World Health Organization; **TB** – tuberculosis

Table 2: Lymphadenopathy characteristics in definite and probable cases of DRESS stratified by HIV status and concomitant TB (n=20)

Parameter	Total number of patients (n=20)	HIV infected (n=13)	HIV TB co-infected (n=7)
Number of sites			
0	3/20 (15)	0	0
1, n (%)	2/20 (10)	1/13 (8)	0
2, n (%)	9/20 (45)	8/13 (62)	5/7(71)
3, n (%)	6/20 (30)	4/13 (30)	2/7 (29)
Lymph node characteristic			
Soft	5/20 (25)	4/13 (31)	2/7 (29)
Firm and rubbery	12/20 (60)	9/13 (69)	5/7 (71)
Stony hard	0	0	0
Site and size			
Cervical <1cm, n (%)	0	0	0
Cervical 1cm-2cm, n (%)	14/20 (70)	10/13 (77)	6/7
Cervical > 2cm, n (%)	1/20 (5)	1/13 (8)	0
Axillary <1cm, n (%)	0	0	0
Axillary 1cm-2cm, n (%)	12/20 (60)	9/13 (69)	6/7
Axillary >2cm, n (%)	1/20 (5)	1/13 (8)	1/7
Inguinal <1cm, n (%)	0	0	0
Inguinal 1cm-2cm, n (%)	9/20 (45)	7/13 (54)	2/7
Inguinal >2cm, n (%)	1/20 (5)	1/13 (8)	1/7

Abbreviations: HIV – Human Immunodeficiency virus; **TB** – tuberculosis

Table 3: Lymphadenopathy site pattern in patients with probable and definite DRESS stratified by HIV status and concomitant TB (n=17 with lymphadenopathy in at least 1 site)

Site	Total number of patients (n=17)	HIV infected (n=13)	HIV uninfected (n=4)	HIV infected+ TB (n=7)
Cervical only	2/17 (12)	1/13 (8)	1/4 (25)	0
Axillary only	0	0	0	0
Inguinal only	0	0	0	0
Epitrochlear only	0	0	0	0
Popliteal only	0	0	0	0
Cervical + axillary	5/17 (29)	4/13 (31)	1/4 (25)	4/7 (57)
Cervical + inguinal	2/17 (12)	2/13 (15)	0	0
Axillary + Inguinal	2/17 (12)	2/13 (15)	0	1/7(14)
Cervical + axillary + inguinal	6/17 (35)	4/13 (31)	2/4 (50)	2/7 (29)

Abbreviations: HIV – Human Immunodeficiency virus; **TB** – tuberculosis

Table 4: Demographics and clinical characteristics of the hospitalized controls without DRESS (n=10)

Variables	All (n=10)
Age in years, median (IQR)	43.5 (38-46)
Gender	
Male, n (%)	4 (40)
Female, n (%)	6 (60)
HIV status	
HIV infected, n (%)	10/10 (100)
WHO clinical stage 3 and 4, n (%)	5/10 (50)
Median CD4 cell count (IQR) cells/mm^3	201 (123-575)
TB	
Pulmonary TB, n (%)	2/10 (20)
Disseminated TB, n (%)	3/10 (30)
HIV and TB, n (%)	5/10 (50)
Co-morbidities	
Diabetes Mellitus, n (%)	1/10 (10)
Hepatitis B infection, n (%)	1/10 (10)
Cardiac failure, n (%)	1/10 (10)
Iron deficiency Anaemia, n (%)	1/10 (10)
Granulomatous inflammation, n (%)	1/10 (10)

Abbreviations: IQR – interquartile range; **HIV** – Human Immunodeficiency virus; **WHO** – World Health Organization. **TB** – tuberculosis

Table 5: Lymphadenopathy in the controls stratified by HIV status and concomitant TB (n=10)

Number of sites	Total number of patients (n=10)	HIV infected with no TB (n=5)	HIV infected + concomitant TB (n=5)
0	7/10 (70)	4/5 (80)	3/5 (60)
1, n (%)	3/10 (30)	1/5 (20)	2/5 (40)
2, n (%)	2/10 (20)	1/5 (20)	1/5 (20)
3, n (%)	2/10 (20)	1/5 (20)	1/5 (20)

Abbreviations: HIV – Human Immunodeficiency virus; **TB** – tuberculosis

SUPPLEMENTARY TABLES

Supplementary Table 1: Lymphadenopathy site pattern in the controls stratified by HIV status and concomitant TB (n=5)

Site	Total number of patients (n=5)	Pulmonary TB (n=2)	Disseminated TB (n=3)
Cervical, n (%)	1/5 (20)	1/2 (50)	0
Axillary, n (%)	0	0	0
Inguinal, n (%)	0	0	0
Epitrochlear, n (%)	0	0	0
Popliteal, n (%)	0	0	0
Cervical + axillary, n (%)	0	0	0
Cervical + inguinal, n (%)	0	0	0
Axillary + Inguinal, n (%)	0	0	0
Cervical + axillary + inguinal, n (%)	1/5 (20)	0	1/3 (33)

Abbreviations: TB – tuberculosis

Supplementary Table 2: Lymphadenopathy size and characteristics in controls stratified by HIV status and concomitant TB (n=3)

Patients with lymph node involvement	Patient 1 (HIV + Pulmonary TB)	Patient 2 (HIV + Disseminated TB)	Patient 3 (HIV)
Site of involvement	Cervical	Cervical, Axillary + Inguinal	Cervical, Axillary + Inguinal
Size of palpated lymph nodes	<1cm	1-2cm	1-2cm
Characteristics of lymph nodes	Firm + rubbery	Firm + rubbery	Shotty
Tenderness on palpation	None	None	None

Abbreviations: TB – tuberculosis; **HIV** - Human Immunodeficiency virus

Annexure 1: RegiSCAR validation scoring for DRESS[10]

Score	-1	0	1	2	Min	Max
Fever ≥ 38°C	N/U	Y			-1	0
Enlarged lymph nodes		N/U	Y		0	1
Eosinophilia Eosinophil count		N/U	 0.7-1.499 × 10^9 L^{-1}	 ≥1.5 × 10^9L^{-1}	0	2
Atypical lymphocytes		N/U			0	1
Skin involvement Skin rash extent (% body surface area) Skin rash suggesting DRESS Biopsy suggesting DRESS	 N N	 N/U U Y/U	 ≥50% Y		-2	2
Organ involvement* Liver Kidney Lung Muscle/heart Pancreas Other organs		 N/U N/U N/U N/U N/U N/U	 Y Y Y Y Y Y		0	2
Resolution ≥ 15 days	N/U	Y			-1	0
Evaluation of other potential causes Antinuclear antibody Blood culture Serology for hepatitis A/B/V Chlamydia/mycoplasma If none positive and ≥ 3 of the above negative			 Y		 0	 1
Total score					-4	9

UNIVERSITY OF CAPE TOWN
Faculty of Health Science■
Human Research Ethics Committee

Room E53-415 Old Main Bulldlng
Groote Schuur Hospltal
Observvatory 7925
Telephone [021] 406 6626
Emall: shuretta.thomas@uct.ac.za
Website: www.bealth.uct.ac.za/fbs/researcb/buwanethlcs/forms

17 September 2018

HREC REF: 578/2018

A/Prof Rl Lehloenya
Dermatology
G13,NGSH

Dear A/Prof RJ Lehloenya

PROJECT TITLE: ASSESSMENT OF LYMPHADENOPATHY IN PATIENTS WITH DRUG REACTION AND EOSINOPHILIA (DRESS): A COMPARATIVE, DESCRIPTIVE STUDY (Masters Candidate - Dr MS Machona)

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

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

Approval Is granted for one year untll the 30 September 2019.

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

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethlcal conduct of the study remains the responsibility of the prlnclpal Investigator.

Please note that for all studies approved by the HREC, the prlnclpal Investigator **m.llll** obtain appropriate institutional approval, where necessary, before the research may occur.

The *HREC acknowledge that* the *student Dr Musonda Sharon Machona wlll also* be *Involved In this study.*

Youn sincerely

pgg LQS:I!il!IAI!I
CHAIRPERSON, fHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Instltutional 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 Cllnlcal 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), South African Good Cllnlcal Practice Guldellnes (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines **(ABPI),** and Declaration of Helsinki (2013) guldellnes.

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 SO, 56 and 312.

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

HUMAN RESEARCH ETHICS COMMITTEE
0 8 DEC 2021
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)

This serves as notification of annual approval, including documentation described below.

☑ Approved	Annual progress report	Approved until/next renewal date 11.22
☐ Not approved	See attached comments	
Signature Chairperson of the HREC/ Designee		Date Signed /, 1.../It,1j

Note: Please email this form and supporting do
hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Excellent progress. The student is completing the final write-up and needs a single folder to review to complete the data collection. Thank you for the declaration document

Principal Investigator to complete the following:

1. Protocol information

Date (when submittino this form)	29/11/2021		
HREC REF Number	578/2018	Current Ethics Approval was granted until	November 2020
Protocol title	Assessment of lymphadenopathy in patients with drug reaction and eosinophilia (DRESS): A comparative, descriptive study		
Protocol number (if aoolicable)			
Are there any sub-studies linked to this study?	☐ Yes	☒ No	
Ifyes, could you please provide the HREC Reference number for all sub-studies? **Note: A** separate FHS016 must be submitted for each sub-study.			

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

Principal Investigator	NProf RJ Lehloenva
Department / Office Internal Mail Address	Ward G23, Division of Dermatology, Department of Medicine

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

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

1.3 Ethics Renewal Fee

Please (tick)appropriate box for billing purposes:

Sug,mi§.sion I l!	*DI!SCriotlgn*	*Newfeg (Vat Incl.J*	*tick*
Research funded solely from UCT departmental/ divisional/group budaet	Annual evaluation of research progress report for re-certification	**R0,00**	D
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleaes	Annual evaluation of research progress report for re-<:ertification	**R0,00**	
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Aooroval	**R7000,00**	D
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress reoort for re-certification for Ex=dited review	**R3 710.00**	D
Annual re-certification / Progress report {FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Aooroval	**R6000,00**	D
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Exoedited review	**R1 500,00**	D

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

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

1. Invoice billing - Directly to Sponsor

Sponsor's name

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

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

2. List of documentation for approval

- Study deviation form

3. Protocol status (tick }

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

4. Enrolment

Number of participants enrolled to date	25
Number of participants enrolled, since last HREC Progress report {continuing review)	2
Additional number of participants still required	0

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

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	**25**
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	25
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
The study has progressed well despite unforeseen circumstances such us the COVID-19 pandemic. We managed to enrol 25 participants in the study and are currently at data analysis and write-up stage of the research. Since the last annual report, we enrolled an extra 2 patients. Unfortunately, there was a reduction in number of patients admitted to the hospital as well as a reduction in out-patient clinics since March 2020 due to the declaration of a Nationwide lockdown in South Africa. We therefore experienced a decrease in our enrolments and could not conduct follow up clinics at 6 weeks as intended. The Masters candidate Dr Machona suffered personal loss from COVID-19 related death of her father and this led to delay in application for the annual renewal of the protocol.

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

	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledoed or aooroved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not vet reported, are attached for review

9. Amendments (tick all that apply)

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

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

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
We were unable to follow up patients enrolled in 2020 at the 6 week follow up drug/allergy clinic as out-patient clinics were shut down due to the pandemic.

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

11. Summary of Monitoring and Audit Activities (tick)

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

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

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

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

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

12. Level of risk (tick)

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

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

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

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick)**			
☐ Yes		No	
Ifyes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via crc@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

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

15. Signature

My signature certifies that the above is complete and correct.			
Signature of Pl		Date	29/11/2021

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

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	17/12/64

Note: Please note that incomplete submiss swill n be reviewed.
Please email this form and supporting documents (if pplicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

HUMAN RESEARCH ETHICS COMMITTEE
0 8 DEC 2021
UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES

1. Protocol information

Date (when submittin!'.lthis form)	29/11/2021
HREC REF Number	578/2018
Project Title	Assessment of lymphadenopathy in patients with drug reaction and eosinophilia-(DRESS): A comparative, descriptive study
Protocol number (if aoolicable)	
Principal Investigator	A/Prof RJ Lehloenya
Department / Office Internal Mail Address	Ward G23, Division of Dermatology, Department of Medicine

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.

The Masters candidate Dr Machona suffered personal loss from COVID-19 related death of her father and her mother was admitted with COVID-19 in ICU for several months. This led to delay in application for the annual renewal of the protocol as she had to travel to Zambia to take care of her mother.

We were unable to follow up patients enrolled in 2020 at the 6 week follow up drug/allergy clinic as out-patient clinics were shut down due to the pandemic.

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.

- An application to renew the protocol has been made.
- In the write-up of the dissertation, the candidate will mention the lack of follow up of a few patients as a study limitation due to the oandemic

3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.

Applications for renewal will be made on time in line with the regulations of the HREC

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.			
Signature of PI		Date	2021/11/29

Western Cape Government

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

PROFESSOR RJ LEHLOENYA
MEDICINE: DERMATOLOGY

E-mail: musondamachona@gmail.com

Dear Professor Lehloenya

RESEARCH PROJECT: Assessment of Lymphadenopathy in Patients with Drug Reaction and Eosinophilia (DRESS): A Comparative, Descriptive study

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 November 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 3 February 2022

C.C. Mr. L. Naidoo, Dr. N. Khumalo, Prof. N. Ntusi, Mr. A. Mohamed

TITLE OF THE RESEARCH PROJECT: Lymphadenopathy in patients with DRESS syndrome

HREC REFERENCE NUMBER: 578/2018

PRINCIPAL INVESTIGATOR: Rannakoe J Lehloenya, MBChB, FCDerm (SA)

CO-INVESTIGATORS: Musonda Sharon Machona MBChB, Rudzani Muloiwa MBChB, DCH, MSc, FCPaeds (SA)

ADDRESS: G23, Groote Schuur Hospital, Main Road, Observatory, 7935

CONTACT NUMBER: 021-404-3376

You are being invited to take part in a research project. Please take some time to read this information, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study about?

This is a study about patients admitted to the dermatology departments at Red Cross Children's Hospital and Groote Schuur Hospital with a drug reaction with eosinophilia and systemic symptoms also known as DRESS. DRESS is a severe reaction to an ingested medication that is characterized by a rash and internal organ involvement. The cause of DRESS is not well established but reduced immunity, certain genes and reactivation of viruses such as herpes may predispose individuals to develop this condition. The commonest drugs associated with this reaction include medications used for treatment of Tuberculosis, Epilepsy and Human Immunodeficiency Virus (HIV) infection (Anti-retrovirals).

DRESS occurs in both children and adults as an eruption of skin lesions associated with fever, swollen lymph nodes, abnormalities in blood cell counts and multi-organ manifestations (the liver, kidneys, gut). A lymph node is a small, bean-shaped mass of tissue that helps the body to fight infections. Some are located in deep tissue, while others are located in clusters closer to the skin (eg the neck, armpits, elbows, groin and behind the knees) and can be easily felt when they are swollen.

The study aims to find out how many people with DRESS will have swollen lymph nodes. The study involves being examined by a doctor to check for any swollen lymph nodes that are located close to the skin on your body. The doctor will palpate different areas on your body suck as the neck, armpits,

elbows, groin area and behind your knees. If you have never been tested for HIV, you will be asked if your blood can be tested.

Why have you been invited to participate?

You have been asked to participate because you have developed a reaction (DRESS) to a medication that you took and have been admitted by our dermatology department.

What will your responsibilities be?

You will be asked to allow a doctor to examine you for swollen lymph nodes on your body.

Will you benefit from taking part in this research?

There are no direct benefits from taking part in the research. You will not get personal feedback on results. We will present our results to the dermatology doctors working at the Red Cross and Groote Schuur Hospitals and aim to publish the results in a medical journal. This will improve our knowledge of individuals that react to certain medication. You will remain anonymous.

Are there in risks involved in your taking part in this research?

We do not anticipate any significant risks to taking part. Your information will be kept confidential.

If you do not agree to take part, what alternatives do you have?

Your participation is entirely voluntary. If you have DRESS and choose not to participate, you will still be seen by a doctor in the ward as usual.

Who will have access to your medical records?

You will be given a participant ID number and this will be used instead of your name or hospital number for data capture and laboratory analysis to ensure confidentiality.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

We do not anticipate any injury occurring. However if a problem occurs, you will be referred to the nearest appropriate facility.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to participate.

Is there anything else that you should know?

You can contact the Health Research Ethics Committee **at 021-404-7682 or 021-406-6338** if you have any concerns or complaints that have not been adequately addressed by your study doctor. You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I _____ agree to take part in a research study entitled Lymphadenopathy in patients with DRESS syndrome

I am the parent or guardian of (child's name) _____ **and agree that he/ she may take part.**

- I declare that:
- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signature of participant: _____ Date: _____

Signature of witness: _____ Date: _____

Declaration by investigator

I (name) _____ declare that:

- I explained the information in this document
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.
- I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.
- If participation of a minor is involved, I obtained verbal assent from him/her.

Signature of investigator: _____ Date: _____

Signature of witness: _____ Date: _____

TITLE OF THE RESEARCH PROJECT: Lymphadenopathy in patients with DRESS syndrome

HREC REFERENCE NUMBER: 578/2018

PRINCIPAL INVESTIGATOR: Rannakoe J Lehloenya, MBChB, FCDerm (SA)

CO-INVESTIGATORS: Musonda Sharon Machona MBChB, Rudzani Muloiwa MBChB, DCH, MSc, FCPaeds (SA)

ADDRESS: G23, Groote Schuur Hospital, Main Road, Observatory, 7935

CONTACT NUMBER: 021-404-3376

What is RESEARCH?

Research is something we do to find new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about disease or illness. Research also helps us to find better ways of helping, or treating children who are sick.

What is this research project all about?

This is a study that will involve children that are admitted to hospital after their body has reacted to a certain medication that they were given to make them feel better. The reaction can include developing bumps or lumps under the skin (in the neck, armpits, elbows, private area or behind the knees) which are called lymph nodes, fever, abnormal number of soldier cells that fight against infection in the blood or it can also hurt the liver, kidneys and the gut.

Why have I been invited to take part in this research project?

You have been invited to take part because you have developed a reaction to a medication that you drunk.

Who is doing the research?

I am a medical doctor who works at both Red Cross and Groote Schuur Hospitals. I am doing this project as part of my training to become a doctor that sees children and adults who have diseases that affect their skin.

What will happen to me in this study?

In this study a doctor will check your body for any swollen lymph nodes which are bumps or lumps that the doctor can feel on certain parts of your body like your neck, armpits, elbows, private area and behind your knew.

Can anything bad happen to me?

Nothing bad will happen to you if you choose to participate in this study. Sometimes when the doctor uses their hand to feel for the bumps and lumps you might feel uncomfortable, ticklish in the armpits or some pain if they press to hard. Please tell your parents or guardians if you are in pain because of being in the study.

Can anything good happen to me?

Nothing good will happen to you because you are in the study. You will still receive all your treatments so that you feel better even if you choose to not be part of the study. However you agreeing to be in the study will help us know better about children that react to medication like you did.

Will anyone know I am in the study?

No one will know that you were in the study as your name will not be revealed to anyone. You will be given a number that will be used as your identity.

Who can I talk to about the study?

Your parent or guardian can contact the Health Research Ethics Committee **at 021-404-7682 or 021-406-6338** if you have any concerns or complaints that have not been answered by your study doctor

What if I do not want to do this?

It is ok if you do not want to do this. You will not get into any trouble for it even if your parents have agreed and you refuse. If you agree to be part of the study, you will still be free to withdraw at any time.

Do you understand this research study and are you willing to take part in it?

YES	NO

Has the researcher answered all your questions?

YES	NO

Do you understand that you can pull out of the study at any time?

YES	NO

Signature of Child _____ Date _____

TITLE OF THE RESEARCH PROJECT: Lymphadenopathy in patients with DRESS syndrome

HREC REFERENCE NUMBER: 578/2018 Version1.2 Controls

PRINCIPAL INVESTIGATOR: Rannakoe J Lehloenya, MBChB, FCDerm (SA)

CO-INVESTIGATORS: Musonda Sharon Machona MBChB, Rudzani Muloiwa MBChB, DCH, MSc, FCPaeds (SA)

ADDRESS: G23, Groote Schuur Hospital, Main Road, Observatory, 7935

CONTACT NUMBER: 021-404-3376

You are being invited to take part in a research project. Please take some time to read this information, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study about?

This is a study about patients admitted to the dermatology departments at Groote Schuur Hospital with a drug reaction with eosinophilia and systemic symptoms also known as DRESS. DRESS is a severe reaction to an ingested medication that is characterized by a rash and internal organ involvement. The cause of DRESS is not well established but reduced immunity, certain genes and reactivation of viruses such as herpes may predispose individuals to develop this condition. The commonest drugs associated with this reaction include medications used for treatment of Tuberculosis, Epilepsy and Human Immunodeficiency Virus (HIV) infection (Anti-retrovirals).

DRESS occurs in both children and adults as an eruption of skin lesions associated with fever, swollen lymph nodes, abnormalities in blood cell counts and multi-organ manifestations (the liver, kidneys, gut). A lymph node is a small, bean-shaped mass of tissue that helps the body to fight infections. Some are located in deep tissue, while others are located in clusters closer to the skin (eg the neck, armpits, elbows, groin and behind the knees) and can be easily felt when they are swollen.

The study aims to find out how many people with DRESS will have swollen lymph nodes. The study involves being examined by a doctor to check for any swollen lymph nodes that are located close to the skin on your body.

You have not reacted to any medication and do not have DRESS. However, we need your help because you are being treated for HIV and TB infections. We would like to see if you also have swollen

lymph nodes due to HIV infection or Tuberculosis (TB). This will help us determine if the swollen lymph nodes in patients with DRESS syndrome happen only because of the drug reaction or they can happen because of other infections that these patients may have at the same time as the drug reaction. The doctor will palpate different areas on your body suck as the neck, armpits, elbows, groin area and behind your knees. If you have never been tested for HIV, you will be asked if your blood can be tested.

Why have you been invited to participate?

You have been asked to participate because even though you did not develop a drug reaction (DRESS) to a medication that you took, you are being treated for HIV and TB.

What will your responsibilities be?

You will be asked to allow a doctor to examine you for swollen lymph nodes on your body.

Will you benefit from taking part in this research?

There are no direct benefits from taking part in the research. You will not get personal feedback on results. We will present our results to the dermatology doctors working at Groote Schuur Hospital and aim to publish the results in a medical journal. This will improve our knowledge of individuals that react to certain medication. You will remain anonymous.

Are there in risks involved in your taking part in this research?

We do not anticipate any significant risks to taking part. Your information will be kept confidential.

If you do not agree to take part, what alternatives do you have?

Your participation is entirely voluntary. If you have HIV and TB and choose not to participate, you will still be seen by a doctor in the ward as usual.

Who will have access to your medical records?

You will be given a participant I.D number and this will be used instead of your name or hospital number for data capture and laboratory analysis to ensure confidentiality.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

We do not anticipate any injury occurring. However, if a problem occurs, you will be referred to the nearest appropriate facility.

Will you be paid to take part in this study and are there any costs involved?

You will not be paid to participate.

Is there anything else that you should know?

You can contact the Health Research Ethics Committee **at 021-404-7682 or 021-406-6338** if you have any concerns or complaints that have not been adequately addressed by your study doctor. You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I _____ agree to take part in a research study entitled Lymphadenopathy in patients with DRESS syndrome

I am the parent or guardian of (child's name) _____ **and agree that he/ she may take part.**

- I declare that:
- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signature of participant: _____ Date: _____

Signature of witness: _____ Date: _____

Declaration by investigator

I (name) _____ declare that:

- I explained the information in this document
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.
- I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.
- If participation of a minor is involved, I obtained verbal assent from him/her.

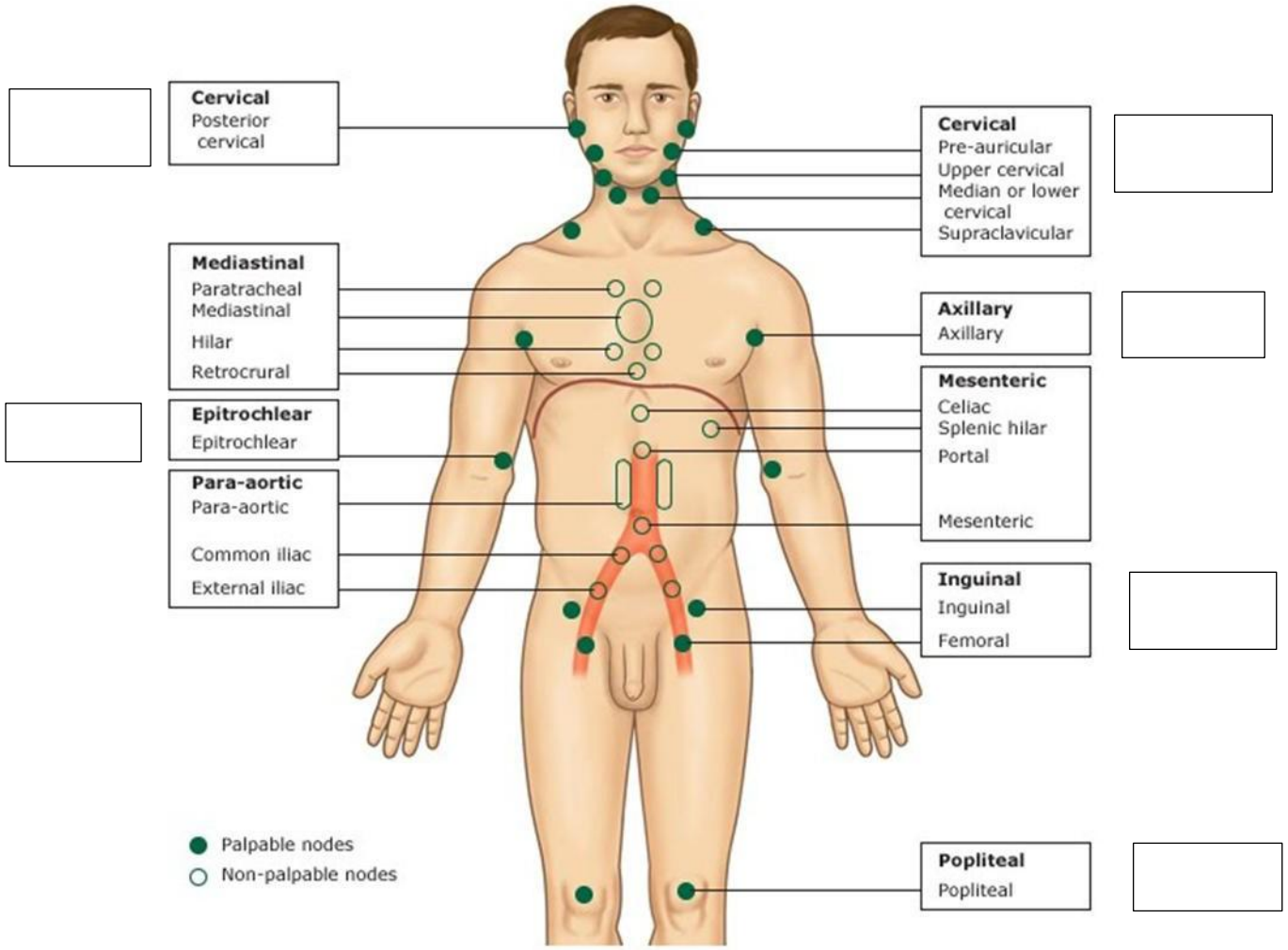
Signature of investigator: _____ Date: _____

Signature of witness: _____ Date: _____

Lymphadenopathy in patients with DRESS syndrome study HREC REF 578/2018

Patient Sticker:

- **Kindly indicate average size of lymph nodes in cms in blank boxes provided#**
- **Character of lymph nodes: Soft ☐ Stony hard ☐ Firm and rubbery ☐ Matted ☐**



- **No Lymphadenopathy ☐**

Examined by: …….. Sign: ……

…… Sign: ……

Author Information

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Introduction

JACI: *Global* is a peer-reviewed, open access, online publication of the American Academy of Allergy, Asthma & Immunology (AAAAI). It joins the other members of the AAAAI family of journals - *The Journal of Allergy and Clinical Immunology* (JACI), the #1 most highly-cited allergy and clinical immunology journal, and JACI: *In Practice*, ranked #3 overall in Allergy (2021 Journal Citation Reports, published by Clarivate Analytics).

As the open access journal for the AAAAI, JACI: *Global* will publish reports describing original research - basic, translational and clinical - related to all aspects of allergy, immunology, and related fields. This very broad scope will mirror the scope of its two companion journals. In addition to translational content, JACI: *Global* will publish basic science, Phase I/II clinical trials, population studies, as well as regionally relevant research relevant to allergy and immunology.

Submission checklist

an use this list to carry out a final check of your submission before you send it to

the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

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For further information, visit our Support Center.

Before You Begin

Ethics in publishing

Please see our information on Ethics in publishing.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

The author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committee(s). This statement should contain the date and reference number of the ethical approval(s) obtained. Authors should also include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

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1. that autonomous consent free from coercion was obtained from the donor(s) or their next of kin; and
2. that organs/tissues were not sourced from executed prisoners or prisoners of conscience.

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Informed consent and patient details

Studies on patients or volunteers (including organ/tissue donors) require informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author, but copies should not be provided to the journal.

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The Corresponding Author is responsible for obtaining each author's statement and all authors should see and approve the complete disclosure before submission to the Journal.

Peer review process

JACI: *Global* operates a single anonymized review process. All contributions will be initially assessed by the Editor-in-Chief for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final

decision regarding acceptance or rejection of articles. The Editor's decision is final. Editors are not involved in decisions about papers which they have written themselves or have been written by family members or colleagues or which relate to products or services in which the editor has an interest. Any such submission is subject to all of the journal's usual procedures, with peer review handled independently of the relevant editor and their research groups.

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Where authors use generative artificial intelligence (AI) and AI-assisted technologies in the writing process, authors should only use these technologies to improve readability and language. Applying the technology should be done with human oversight and control, and authors should carefully review and edit the result, as AI can generate authoritative-sounding output that can be incorrect, incomplete or biased. AI and AI-assisted technologies should not be listed as an author or co-author, or be cited as an author. Authorship implies responsibilities and tasks that can only be attributed to and performed by humans, as outlined in Elsevier's AI policy for authors.

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Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify compliance, your article may be checked by Crossref Similarity Check and other originality or duplicate checking software.

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Reporting Race and Ethnicity

JACI: *Global* encourages the reporting of race and ethnicity in all clinical studies unless the information is not available. Reporting of race and ethnicity should not be considered in isolation but should be accompanied by reporting and discussion of intersecting sociodemographic and social determinant factors. The following guidance is provided to standardize and optimize the reporting of race and ethnicity in the

Journal and is based on updated guidance in the *AMA Manual of Style*.*

- "The names of races, ethnicities, and tribes should be capitalized, such as eg, African American, Alaska Native, American Indian, Asian, Black, Cherokee Nation, Hispanic, Kamba, Kikuyu, Latino, and White."*
- "The term *minorities* should not be used when describing groups or populations because it is overly vague and implies a hierarchy among groups."* Other terms such as *underserved populations, underrepresented populations, marginalized/historically marginalized*, or *historically excluded* may be used as more accurate and descriptive terminology.
- "Racial and ethnic terms should not be used as a noun form (eg, avoid Asians, Blacks, Hispanics, or Whites)."* The adjectival form should be used instead (eg, Asian women, Black patients, Hispanic children, or White participants), which follows AMA style regarding person-first language.
- Do not use the term race/ethnicity but use the term *race and ethnicity* instead.
- Provide an explanation of how participant race and ethnicity was classified "and the source of the classifications used (eg, self-report or selection, investigator observed, database, electronic health record, survey instrument)."*
- Provide an explanation of how participant race and ethnicity was classified and the source of the classifications used (eg, self-report or selection, investigator observed, database, electronic health record, survey instrument).
- "Specific racial and ethnic categories are preferred over collective terms, when possible."* Define what categories are included in groups labeled as *other*. "The terms *multiracial* and *multiethnic* are acceptable in reports of studies if the specific categories these terms comprise are defined or if the terms were predefined in a study or database to which participants self-selected."*
- "Categories should be listed in alphabetical order in text and tables.
- "Race and ethnicity categories of the study population should be reported in the Results section of the manuscript."*
- When appropriate, outcomes should be stratified by race and ethnicity.
- In the Discussion, comment on the overall representatives of the clinical study regarding race and ethnicity and discuss the relevance of any underrepresentation to the condition being studied.

**AMA Manual of Style, Section 11.12.3 Race and Ethnicity. Accessed September 20, 2021. https://www.amamanualofstyle.com*

Reporting Sex and Gender

- The term *sex* should be used when reporting biological factors and *gender* should be used when reporting gender identity or psychosocial/cultural factors.
- The methods used to obtain information on sex, gender, or both (eg, self-reported, investigator observed or classified, or laboratory test) should be explained in the Methods section.
- The sex and/or gender distribution of study participants should be reported in the Results section.
- When appropriate, outcomes should be stratified by sex and/or gender.
- In the Discussion, comment on the overall representatives of the clinical study regarding sex and/or gender and discuss the relevance to the condition(s) being studied.

Reporting sex- and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth (""sex assigned at birth""), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact

and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms ""sex"" and ""gender"" can be ambiguous—thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Authorship requirements

Please note:
(A) To be listed as an author, an individual must meet the requirements approved by the International Committee of Medical Journal Editors (ICMJE). In order to be included in the list of authors, an individual must have done all of the following: (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafted the article or reviewed it critically for important intellectual content; and (3) given final approval of the version to be published.
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All figures submitted must be accurate representations of actual research images. Specific features within an image should not be enhanced, obscured, moved, deleted, or added. Adjustments of brightness, contrast, or color balance are acceptable if applied to the entire image, as long as these techniques do not obscure, eliminate, or misrepresent any information present in the original, including backgrounds (backgrounds should not be faded out to the extent that they are undetectable). If there are any questions about a figure, the Editor may contact the corresponding author at any point, even after the publication of the article.

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Reporting clinical trials

Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram are available online.

Registration of clinical trials

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors recommendations. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

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The systematic allergen nomenclature of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee should be used for manuscripts that include the description or use of allergenic proteins. For manuscripts describing new allergen(s), the systematic name of the allergen must be approved by the WHO/IUIS Allergen Nomenclature Sub-Committee prior to manuscript publication. To avoid the risk of delay of publication, authors are encouraged to apply for a new allergen name using the posted submission form at the WHO/IUIS Allergen Nomenclature website (http://www.allergen.org) before manuscript submission. The systematic nomenclature consists of the first three letters of the taxonomic genus of the allergen source, followed by a space; the first letter of the species epithet, followed by a space; and an Arabic numeral usually indicating the chronological order in which the allergen was described. For example, the first allergen to be purified from the house dust mite, Dermatophagoides pteronyssinus, is named "Der p 1." Further examples of the systematic allergen nomenclature for over 500 allergens can be found at: http://www.allergen.org. The submissions to the Allergen Nomenclature Sub-Committee will be kept confidential until publication if

requested by the authors."

STROBE statement for observational studies

When preparing observational reports, we encourage authors to review the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement, available at www.strobe-statement.org.

PRISMA guidelines for systematic reviews and meta-analyses

For meta-analysis of RCTs, we encourage authors to consult the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, available at www.prisma-statement.org.

STARD statement for diagnostic studies

For reports of diagnostic studies, we recommend the STARD (Standards for Reporting of Diagnostic Accuracy) Statement, available at www.stardstatement.org.

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Suggesting reviewers

Please submit the names and institutional e-mail addresses of several potential reviewers.

You should not suggest reviewers who are colleagues, or who have co-authored or collaborated with you during the last three years. Editors do not invite reviewers who have potential competing interests with the authors. Further, in order to provide a broad and balanced assessment of the work, and ensure scientific rigor, please suggest diverse candidate reviewers who are located in different countries/regions from the author group. Also consider other diversity attributes e.g. gender, race and ethnicity, career stage, etc. Finally, you should not include existing members of the journal's editorial team, of whom the journal are already aware.

Note: the editor decides whether or not to invite your suggested reviewers.

Preparation

NEW SUBMISSIONS

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process.
As part of the Your Paper Your Way service, you may choose to submit your manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or lay-out that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately.

Formatting requirements

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.
If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.
Divide the article into clearly defined sections.

Figures and tables embedded in text

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

REVISED SUBMISSIONS

Use of word processing software

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

As with new submissions, revisions must be submitted electronically through EM (https://www.editorialmanager.com/jacig/default.aspx). Ensure that the revised manuscript is prepared in accordance with the Journal's format and style for the type of article being revised. Please refer to the Journal Article Publishing Support Center (https://service.elsevier.com/app/home/supporthub/publishing/) for additional information. Adherence to these guidelines is important to prevent a delay in processing the revised manuscript.

Revisions must include the following:
(1) A **Responses to Comments** document that includes point-by-point responses to the comments made by the Reviewers, Editor, and Editorial Office. In your Responses to Comments document, reproduce each comment verbatim and in its entirety and follow the comment with your detailed response. Each of the comments should be preceded by the word "COMMENT," and the font style for each comment should be bold. Each of your responses should be preceded by the word "RESPONSE," and the font style for each response should be regular (not bold). In each response, indicate where relevant changes have been made in the manuscript or explain why no changes would be appropriate. If any alterations have been made to your figures or if any figures have been removed or replaced, describe the changes.
(2) A **Marked Manuscript.** The Marked Manuscript should be a version of your revised manuscript in which all of the ways in which it is different from the original manuscript are indicated for the sake of the Editor. The preferred method of indicating changes is Microsoft Word's Track Changes feature. Alternately, any text that has been added should be underlined, and any text that was deleted should be indicated

by strikethrough formatting. Any table that was part of your original submission should be either embedded within the Marked Manuscript or provided as a separate file (e.g., "Table II - Marked"); if changes have been made to the table, they should be indicated. Likewise, any figure that was part of your original submission should be either embedded within the Marked Manuscript or provided as a separate file (e.g., "Figure 1 - Marked"); if changes have been made to the figure, they should be described in your Responses to Comments document. Line numbering (continuous) should be used throughout the Marked Manuscript.
(3) An **Unmarked Manuscript.** The Unmarked Manuscript should be your revised manuscript just as you intend it for publication (if it is accepted). Any table that is to be part of your revised manuscript should be either embedded within the Unmarked Manuscript or provided as a separate file (e.g., "Table II - Unmarked"). Any figure that is to be part of your revised manuscript must be provided as a separate file (e.g., "Figure 1-Unmarked").
(4) **Conflict of Interest Disclosure.**

If there were no changes made to the display items during revision, please re-submit the original display items.

Article structure

Selecting a title for your paper

Please consider the following guidelines:

- Keep the title succinct: Limit it to 12 words or fewer.
- Communicate a single subject or idea in the title.
- Construct the title around the article's key words.
- Include the specific symptom, condition, intervention, mechanism, or function of the paper's central focus.
- Mention any defining population, age, gender, or animal species that distinguishes the work.
- Use terms that are specific rather than general (e.g., "penicillin" rather than "betalactam antibiotic") and include terms that clarify (e.g., "CXCR4" rather than "chemokine receptors").
- Avoid using strong words (such as "robust," "innovative," "significant," "vigorous," and "aggressive"), as they may suggest exaggerated or unwarranted claims.
- Use wit carefully and appropriately; be informative first and clever second. Although a universally understood pun can work well to attract interest, ensure that it will not confuse or mislead the reader.

- The titles of papers accepted for publication in the *Journal of Allergy and Clinical Immunology: Global* may be revised for improved clarity and appeal to the readership. Such revision will have final approval by the authors.

Basic formatting

The title page, abstract, key words, abbreviations, text, acknowledgments, references, and figure legends should be included in a single file (.doc or .docx format). Tables and their legends may be included at the end of the same file (after the reference list and figure legends, if applicable). Alternatively, tables and their legends can be loaded as a separate Tables file.

The generic terms for all drugs and chemicals should be used.

Figures should be uploaded each as separate Figure files, with the figure legends placed in the manuscript file, after the reference list. Tables can either be placed in the manuscript file, after the reference list and figure legends (if applicable), or uploaded as a separate Tables file. Please see the Artwork section for specific formatting information for Figures. Tables need to be created using Microsoft Word's Tables function, and uploaded a .doc file(s).

Article types

The JACI: *Global* will consider publication of several types of manuscripts:

A. Original articles. These articles should describe fully, but as concisely as feasible, the results of original clinical research. Original Articles should not exceed **3,500** words, not including the abstract, figure legends, and references. Each figure legend should be held to **200** words or less. Each Original Article may be accompanied by a total of no more than **8** graphic presentations (tables and/or figures), for example 3 tables and 5 figures.(Additional text, tables, or figures can be designated as "supplemental" material, which will be included in the manuscript's Online Repository.) Please note: Original Article manuscripts that are determined to significantly exceed these limits, or that do not include all of the elements listed below, may be returned to the authors for revision prior to review.

Original Articles should include:
1. Title page. The title should be followed by:

- The list of authors, including their full names, highest academic degrees, and institutional affiliations. Please see the guidelines regarding which contributors should be included in the author list.
- The name, address, telephone number, fax number, and email address of the author who should be contacted regarding the manuscript following its publication. Note: A different author may be designated as the Corresponding Author in the submission system for the duration of the submission and review processes.
- A declaration of all sources of funding for the research reported in the manuscript.
- Please note: The titles of papers accepted for publication in the JACI: Global may be revised for improved clarity and appeal to the readership. Such revision will have final approval by the authors.

2. Structured Abstract. As a general rule, the abstract should be no longer than **250** words. It should summarize the results and conclusions concisely. Tabular data should not be included and acronyms/abbreviations should be avoided or spelled out fully. Abstracts should be structured as follows:

- **Background:** What is the major problem that prompted the study?
- **Objective:** What is the purpose of the study?
- **Methods:** How was the study done?
- **Results:** What are the most important findings?
- **Conclusion:** What is the most important conclusion drawn?

3. Clinical Implications or Key Messages. Provide ONE of the following:

either
• a very brief paragraph (consisting of no more than 30 words) summarizing the diagnostic, therapeutic, or management implications of the article. The heading for this paragraph should be **Clinical Implications.**

or
• (if the article is mechanistic) two or three independent bulleted statements that present the key findings or concepts in the article and comment on their implications. The heading for this small set of bulleted statements should be **Key Messages.**

4. Key words. A list of up to ten key words should follow the Key Messages or Clinical

Implications.

5. Abbreviations. Provide a list of any abbreviations/acronyms and their definitions following the key words. Only standard abbreviations are to be used. If you are uncertain whether an abbreviation is considered standard, consult *Scientific Style and Format* by the Council of Science Editors or the AMA's *Manual of Style*. A laboratory or chemical term or the name of a disease process that will be abbreviated must be spelled out at first mention, the acronym or abbreviation following in parentheses.

6. Text. The manuscript should be written in clear and concise English. Authors whose primary language is not English should obtain assistance with writing to avoid grammatical problems. The text should be organized in sections as follows: Introduction, Methods, Results, and Discussion. Each section should begin on a new page. The generic terms for all drugs and chemicals should be used.

In studies involving human subjects, a statement describing approval by the appropriate Institutional Review Board is required. Studies involving experimental animals must include a statement in the Methods section indicating which guidelines were followed for the care and use of the animals (e.g., the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research or the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press [revised 1996]).

7. Acknowledgments. General acknowledgments for consultations, statistical analyses, and the like should be listed at the end of the text, including full names of individuals involved. However, as noted above, acknowledgment of funding should be listed on the title page.

8. References. It is the Editors' expectation that authors will perform a comprehensive search of the literature to gather the most current articles relative to the subject matter. All references that are five years old or more should be replaced with current literature, unless the referenced publication is a classic work that underscores the core subject.

Brief reports

B. A brief report is a submission that conveys a research, observation or finding that is novel or unexpected and thus may have an immediate impact on the field. This format is not meant for case reports or case series unless mechanistic studies have been done and led to new concepts or treatments. The review process is as rigorous as

that of an Original Article. A brief report is not meant to be a re-write of an original article with most of the changes deposited in the online repository.

A brief report is 1,500 words long, has a maximum of five display items (figures and/or tables), and a maximum of 25 references. Online Repository content may be used for additional information on Methods.

The structure of a brief report includes a structured abstract of no more than 250 words, an introduction, and one section for combined results and discussion. For example:

Additional sections will be similar to the Original Articles in terms of formatting. See the Original Article section for information on:
1. Title Page:
a) Title - up to 12 words
b) Authors (given name(s), surname(s), highest academic degree(s))
c) Author institutional affiliations
d) Corresponding Author (mailing address, phone number and email address)
e) Funding Statement (see above section "Role of the Funding Source")
f) Disclosure Statement (must include ALL authors - see above section "Conflict of Interest")
2. Abstract. As a general rule, the abstract should be no longer than 250 words. It should summarize the results and conclusions concisely. Tabular data should not be included and acronyms/abbreviations should be avoided or spelled out fully. Abstracts should be structured as follows:

- **Background:** What is the major problem that prompted the study?
- **Objective:** What is the purpose of the study?
- **Methods:** How was the study done? Also include the text "For detailed Methods, please see the Methods section in this article's Online Repository at www.jacionline.org"
- **Results:** What are the most important findings?
- **Conclusion:** What is the most important conclusion drawn?

3. Clinical Trial registration if applicable (see "Clinical Trial Results" section above)
4. Clinical Implications (maximum 30 words) or Key Messages (2-3 short bullet points)
5. Key Words (up to 10)
6. Abbreviations
7. Main Text (maximum 1500 words)
a) Structured headings

- Introduction
- Results and Discussion

8. Acknowledgments (if applicable)
9. References (maximum 25; Vancouver style)
10. Tables (editable Word documents; no images or color
11. Figure Legends (maximum 60 words each)
12. Online Repository

- Online Repository Text limited to Methods only
- References (Vancouver style)
- Tables (only if related to Methods, labeled Table E1, etc.)
- Figures (may only be used if related to Methods; each Figure uploaded separately named E1, E2, etc without embedded legends)
- Figure Legends (include in repository text file, labeled Figure E1, etc.)

Correspondence and replies

C. JACI: *Global* accepts two kinds of Correspondence: a. Correspondence related to papers published in JACI: *Global*, and b. Correspondence which is NOT related to papers published in JACI: *Global*.

1. Correspondence related to papers published in JACI: *Global* must be received within one month of publication of the paper in question. If the correspondence is considered acceptable, a response will be requested from the authors of the original paper for an optional Reply, for publication alongside the Correspondence.

2. Correspondence which is NOT related to papers published in JACI: *Global* should be reserved for communications regarding current issues in Allergy/Immunology.

Correspondence manuscripts must:
(1) Be no longer than 500 words.
(2) Have a short, relevant title, distinct from the title of the referenced article. Please note that all Replies should have the title "Reply to [Corresponding author's name]."
(3) Have a complete title page (see section A1).
(4) List the references as complete bibliographic citations at the end of the letter with

the journal article being discussed as the first reference (see section A9 for formatting). The total number of references should be no more than five. Replies should include the Correspondence to which they are replying as one of the references.
(5) Have no more than one graphic presentation (table or figure). (See the section on Graphic Presentations below).
(6) Begin with the salutation "To the Editor:" and close with the author's name(s), academic degree(s), institutions(s), and location(s).
(7) No online appendix or supplementary material is allowed.

Review articles

D. Review articles published in the Journal are invited by the Editors. Proposals for review articles may be emailed to the Editorial Office (JACIGlobal@aaaai.org), but current space constraints do not usually allow for the acceptance of unsolicited review manuscripts.

Rostrum articles

E. Opinion articles about subjects of particular interest and/or debate may be accepted for peer review after preliminary review by the Editor. Proposals for rostrum articles may be emailed to the Editorial Office (JACIGlobal@aaaai.org); they will be evaluated based on level of interest, novelty, and the current needs of the Journal.

Case reports

F. Case reports: Case reports focused on novel or difficult cases or descriptions of regional practices will be of particular interest in the Journal. Case Reports are brief reports of clinical or laboratory observations or case series. Single case reports will only be considered if they demonstrate a novel, impactful insight. Like Original Articles, these manuscripts are subject to peer review. A Case Report must:

1. Be brief. A Case Report should not exceed **1,000** words, not including the figure legend(s) and references. The figure legend(s) should be held to **60** words or less.
2. Have a short, relevant title.
3. Have a complete title page.
4. Provide 1-2 sentences (maximum **40** words) that summarize the importance of the report.
5. Have no more than **9** references.

6. List the references as complete bibliographic citations following the end of the letter body.
7. Be limited to a total of **2** figures and/or tables. (An additional **2** figures or tables may be placed in the article's Online Repository).
8. Not have references in the Online Repository.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Structured abstract

A structured abstract, by means of appropriate headings, should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations.

Graphical abstracts

A graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. The submission of a graphical abstract is optional for JACI: *Global*, but is encouraged as it draws more attention to the online article. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files.

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be

presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

Artwork

Electronic artwork

General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Indicate per figure if it is a single, 1.5 or 2-column fitting image.
• For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
• Please note that individual figure files larger than 10 MB must be provided in separate source files.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.

TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi.

TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi.

TIFF (or JPG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.

Please do not:

• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.
• Supply files that are too low in resolution.
• Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF) or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites). Further information on the preparation of electronic artwork.

Figures

If illustrations appear in the manuscript, they must be submitted in electronic format along with the rest of the manuscript. Each figure should be submitted as a separate electronic file, and should not be inserted into the file containing the text of the manuscript.

Figure legends

Figure legends should be listed in the manuscript file, on a separate page after the tables. They should not appear in the figure files. The figure legend will be included when sizing the figure and its length must therefore be taken into consideration. The figure title should appear at the beginning of each legend. The legends themselves should be succinct (no more than 200 words), identifying the data or subject being presented, but not explaining methods or results. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Permission to reuse previously published materials

If applicable, authors of manuscripts submitted to JACI: *Global* must provide the Editorial Office with proof of permission to reuse any previously published material that has appeared in another publication. Additionally, in the case of photographs of identifiable persons, a signed release showing informed consent must be provided. Wording in the permissions form/release should specify "permission to publish in all forms and media." Upon obtaining written permission to reuse the specified material, forward the documentation to the Editorial Office by email (JACIGlobal@aaaai.org). Acceptance of a manuscript is conditional upon receipt of permission.
Please note: It sometimes takes up to 6-8 weeks to obtain permissions from a

publisher, so be sure to allow plenty of time.

Tables

If tables appear in the manuscript, they must be included in the electronic submission. They may be placed within the manuscript file or loaded as separate files (in .doc or .docx format). Tables should supplement, not duplicate, the text; they should be on separate pages, one table per page, and should be numbered with Roman numerals in order of mention. A brief title should be provided directly above each table. Any abbreviations should be defined at the bottom of the table. When creating a table, use the word-processing program's table formatting feature; otherwise, use only tabs (not spaces) to align columns.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, Crossref and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the

format of such citations should be in the same style as all other references in the paper.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Preprint references

Where a preprint has subsequently become available as a peer-reviewed publication, the formal publication should be used as the reference. If there are preprints that are central to your work or that cover crucial developments in the topic, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including the word preprint, or the name of the preprint server, as part of the reference. The preprint DOI should also be provided.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software

Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley. Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes from different reference management software.

Reference formatting

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

Reference style

References should follow "Vancouver style." See the examples below, or http://www.nlm.nih.gov/bsd/uniform_requirements.html for more information. Manuscripts in preparation, personal communications, and other unpublished information should not be cited in the reference list but may be mentioned in the text in parentheses. The references must be identified in the text by superscript Arabic numerals and numbered in consecutive order as they are mentioned in the text. The list of references, in numeric sequence, should be typed at the end of the article. In the submitted version of the manuscript, references should not appear as footnotes or endnotes, and if you have used a program such as EndNote or Reference Manager to create them, the links between the reference numbers and the citations must be removed using the following steps:

(1) Using the "Select All" feature (Ctrl-A for PCs. Cmd-A for Macs), highlight the entire text of the file, including the references.
(2) Use the keystroke command Ctrl-6 for PCs or Cmd-6 for Macs.
(3) Save. This will remove the links (permanently) without disturbing the reference numbers or the citations. It is recommended that you save one copy of your manuscript with the EndNote links in place (for your reference) and one copy of your manuscript without the EndNote links (for submission purposes).

Please note that inclusive page numbers are required. List all authors' names when there are six or fewer; when there are seven or more, list the first six and add "et al."

Examples of Reference Formatting

Journal article:
Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernyobyl: 5-year follow-up. Br J Cancer 1996;73:1006-12.

Book:
Ringsven MD, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Chapter in a book:
Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Internet resource:
US positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, DC: Committee on Government Reform; 2002. Available at: http://www.house.gov/reform/min/inves_tobacco/index_accord.htm. Accessed March 4, 2002.

Dataset
Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.

Journal abbreviations source

Journal names should be abbreviated according to the List of Title Word Abbreviations.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and

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Response to Reviewers and Editorial office R2

Response to Query 1: The title is still not entirely descriptive of the study. Do you not mean to say that advance HIV does not impact the ability to utilize lymphadenopathy in the assessment of DRESS in HIV and TB?

Response 1: Thank you for suggestion and we agree with the reviewer that the suggested title is clearer, and manuscript title has been changed accordingly to read: **"**Advanced HIV does not impact the ability to utilize lymphadenopathy in the assessment of DRESS syndrome in HIV and tuberculosis. A prospective comparative study."

Query 2: I suggest that the last sentence should substitute "with" for "in".

Response 2: Thank you for highlighting this and the substitution has been done.

Query 3: Abstract must have sections Background, Objectives, Methods, Results, and Conclusions.

Response 3: The abstract has been restructured accordingly as suggested.

Query 4: Please include a list of Abbreviations and a Capsule Summary.

Response 4: A list of Abbreviations and a Capsule Summary have been included.

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Advanced HIV does not impact the ability to utilize lymphadenopathy in the assessment of DRESS syndrome in HIV and tuberculosis. A prospective comparative study.

Dear Professor Lehloenya,

We are pleased to inform you that your revised manuscript, noted above, has been accepted for publication in *The Journal of Allergy and Clinical Immunology: Global*.
The following items need to be addressed before the manuscript can be transferred to the publisher:

1. It appears that you have used Figure 1 from Blood -(Ref. 18) do you already have permission to use this? If not, please let me know if there is an alternate image you would like to use, or if you will seek permission for its use and any costs. Because JACI Global is an Open Access journal, anyone using this article would need to be able to access the figure and so we typically prefer to use original figures to ensure there are no permission problems. When you seek permission from Blood, please be sure to indicate that it is for an Open Access usage.

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Editor and Reviewer comments:

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Original figure by Musonda Sharon Machona: