Southern African HIV Clinicians Society

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Our Issues, Our Drugs, Our Patients

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Cutaneous Adverse Drug Reactions (CADR) in TB and HIV

Rannakoe J Lehloenya

Division of Dermatology/ Lung Infection and Immunity Unit

Department of Medicine

University of Cape Town

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No conflict of interests to declare

Outline

- Introduction
- Significant types of CADR in TB
- Initial management in acute stage
- Rationale behind rechallenging
- The rechallenge process and its pitfalls
- Special types of TB CADR

- Adverse drug reactions (ADR) contributed to the death of 2.9% of patients in adult medical wards of four geographically diverse hospitals in SA
- Overall mortality rate was 18 per 100 admissions, and 16% of these deaths were ADR related
- Antiretrovirals, antiTB drugs and co-trimoxazole were the most commonly implicated drugs
- Anti-infective-associated ADR is a major cause of mortality in our setting

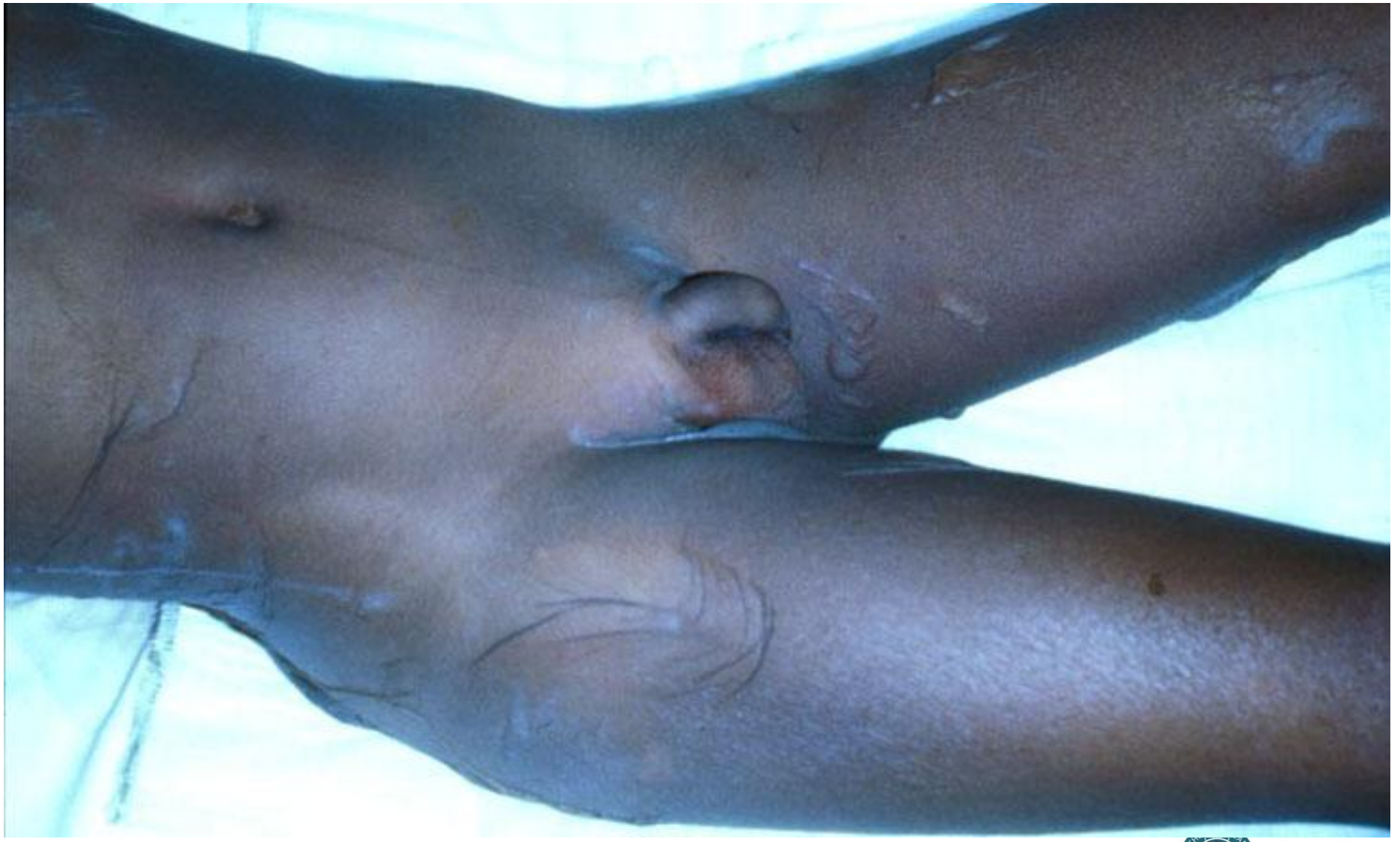
Mouton JP, et al Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol. 2014

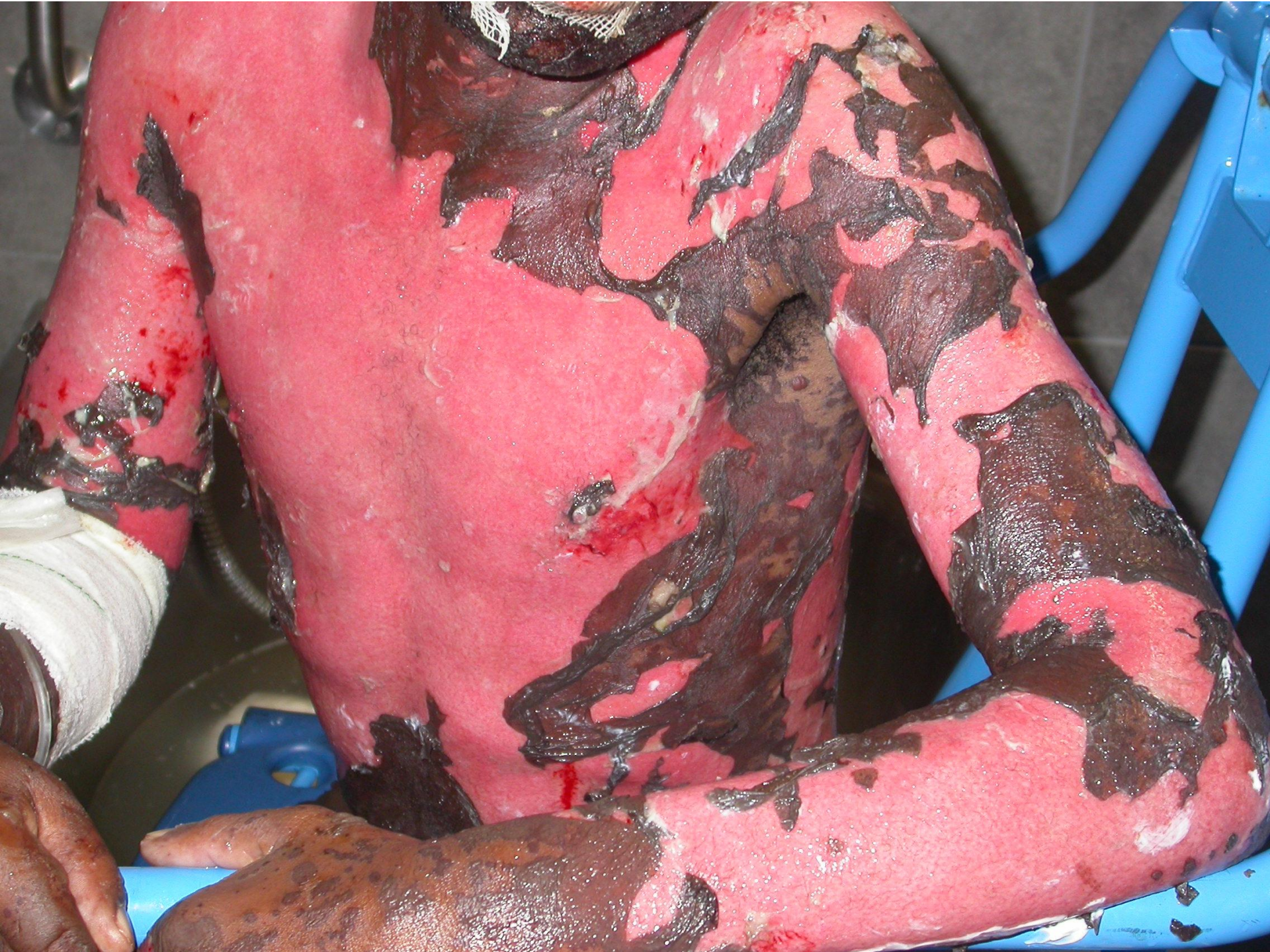
- The incidence of CADR is significantly higher in HIV-infected persons
- However, not all forms of CADR have an increased incidence in HIV
- Urticaria, angioedema, lichenoid drug eruptions, vasculitis and fixed drug eruptions are not more common in HIV-infected persons
- The most common phenotypes in HIV are Stevens Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) accounting for >90% of cases

Lehloenya RJ, Todd G, Badri M, et al. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. Int J Tuberc Lung Dis 2011;15:1649–57.

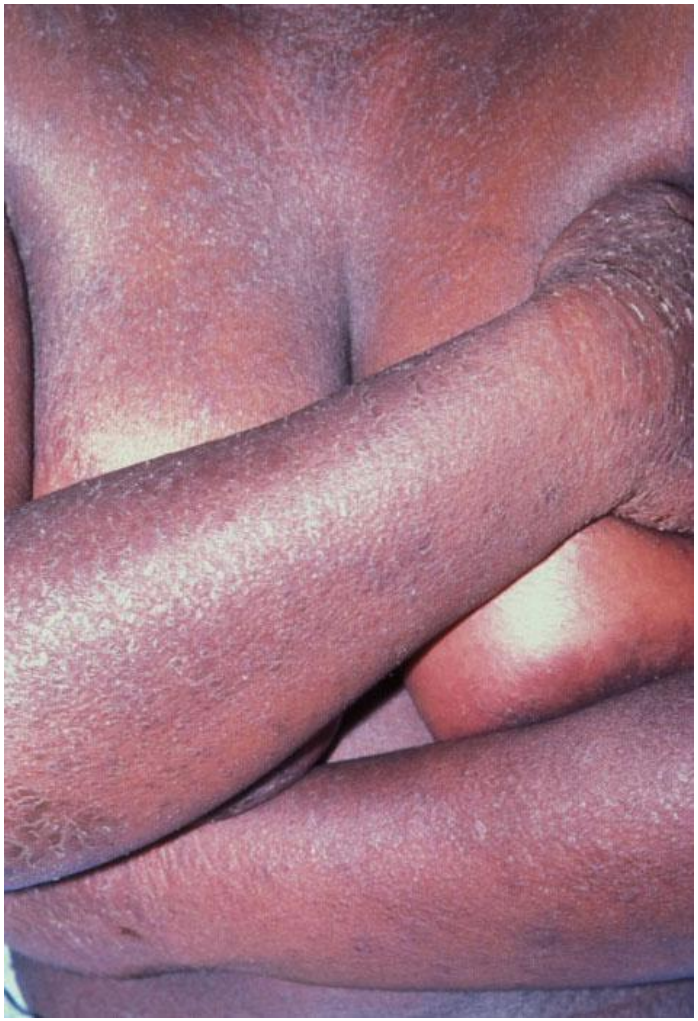
Kannenberg SM, Jordaan HF, Koegelenberg CF, et al. Toxic epidermal necrolysis and Stevens- Johnson syndrome in South Africa: a 3-year pro- spective study. QJM 2012;105:839–46.

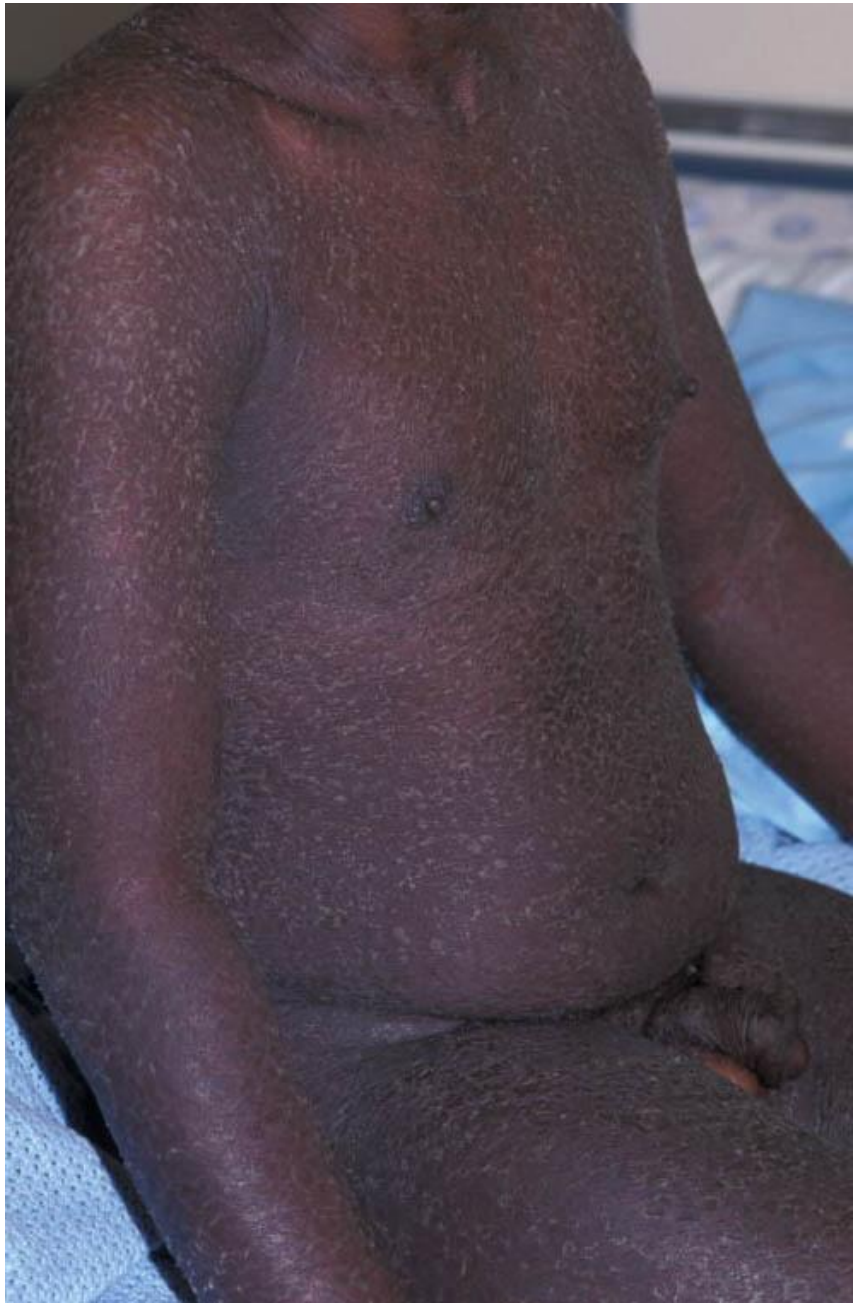
Toxic epidermal necrolysis





Drug Reaction with Eosinophilia and Systemic Symptoms(DHS/DRESS)





Do CADR present differently in HIV?

- No evidence that the reactions are more severe
- No large population studies on mortality and morbidity associated with HIV-associated CADR
- Looking at our data for the last 10 years at Groote Schuur
  - TEN mortality is 9% only on supportive care
  - This compares more than favourably with > 30% in developed countries
- Our population is younger: this may be the explanation for our low mortality

Sekula P, Dunant A, Mockenhaupt M et al. for RegiSCAR study group. J Invest Dermatol. 2013 May;133(5):1197-204

Management of TB-associated CADR

- All anti-TB drugs should be stopped when the initial CADR suspected
- Allow the skin and internal organs to return to a well-documented baseline

Multidisciplinary approach

TB-associated CADRs are multi-organ diseases that often require expertise ranging from hepatologists, infectious disease specialists, pulmonologists, dermatologists, dietitians and others

The best outcomes are attained using a multidisciplinary approach

- **DOES THE PATIENT HAVE TUBERCULOSIS?**
- **ARE YOU AS A CLINICIAN CONFIDENT OF THE DIAGNOSIS OF TUBERCULOSIS?**
- **IS IT WORTH RE-EXPOSING THIS PATIENT TO A POTENTIALLY LIFE-THREATENING DRUG** or can they be managed on 2nd line TB drugs?
- **ARE THE SEQUELAE OF CADR AMENABLE TO THE DRUGS YOU INTEND TO USE?**

Rechallenging first-line drugs in TB-associated CADR

- Rechallenge is a prolonged process
- Median duration of hospitalization is 50 days in our recent study
- 1st initiate a bridge therapy of 3 second-line drugs to which the patient was not previously exposed to minimize risk of resistance

Lehloenya, Dheda. Expert Rev. Anti Infect. Ther 2012

FOR HOW LONG SHOULD I CONTINUE THESE BEFORE INTRODUCING 1ST LINE AGENTS?

INT J TUBERC LUNG DIS 16(9):1260–1264

http://dx.doi.org/10.5588/ijtld.11.0187
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Multiple drug hypersensitivity reactions to anti-tuberculosis drugs: five cases in HIV-infected patients

R. J. Lehloenya,*† J. Wallace,* G. Todd,* K. Dheda†‡

*Division of Dermatology, Department of Medicine, †Lung Infection and Immunity Unit, Division of Pulmonology, University of Cape Town Lung Institute, Department of Medicine, ‡Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

Table Characteristics of rechallenge and subsequent reactions in five patients with MDH

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Drug susceptibility testing	INH-resistant, RMP-susceptible	RMP- and INH-susceptible	RMP- and INH-susceptible	RMP- and INH-susceptible	RMP- and INH-susceptible
Initial treatment for TB	Rifafour*	Rifafour*	Rifafour*	Rifafour*	Rifafour*
Type of initial CADR	DHS	SJS/TEN	DHS	DHS	SJS/TEN
Second-line TB drugs used as cover before rechallenge	OFX, ETH and SM	OFX, ETH and SM	OFX, ETH and SM	OFX, ETH and SM; later AMK due to unavailability of SM	OFX, ETH and SM
Reactions to cover drugs	SM, within 10 min: itch, erythema and facial oedema, followed by generalised burning pain worse on the hands and feet, nausea, increased blood pressure, elevated creatine kinase, hepatitis; nerve conduction studies showed peripheral neuropathy of small fibres OFX, 10 min after ingestion: nausea, burning, generalised pain, painful hands and feet, facial oedema, increased blood pressure	OFX, ETH or SM: fever, headache, itch, conjunctivitis, generalised oedema, burning sensation orally, hepatitis, median sensorimotor neuropathy, peroneal axonopathy, and eosinophilia; these features recurred within 20 min when the 3 drugs were re-introduced; none was re-introduced again	SM: fever; morbilliform rash; conjunctivitis; cheilitis; headache; oedema and palmoplantar erythema within 2 days OFX: within 2 h erythema, rigors, nausea, oedema, tender swollen hands and feet with throbbing pain and conjunctivitis	None	SM: fever, hepatitis and eosinophilia within 3 days OFX: within 30 min after initiation of the drug: itch, erythema and genital pain
Reactions during the rechallenge process to first-line drugs	None	INH: hepatitis, eosinophilia and fever; initial rechallenge was successful and 4 months into therapy, DHS developed which improved on withdrawal of the drugs and recurred on re-initiation. At this point, patient also had CMV retinitis and hepatitis	ETH: itching after a few minutes, erythematous papules on the chest	RMP, after 4 days: erythema, itch, eosinophilia and facial oedema INH, after 3 days: itch, erythema and eosinophilia PZA, after 3 days: hepatitis, itch, facial oedema and eosinophilia	INH: SJS/TEN on oral rechallenge within 3 days
Route of administration leading to reaction	Oral, 1; injection, 1	Oral, 3; injection, 1	Injection, 1; oral, 2	Oral, 2; patch test, 1	Oral, 2; injection, 1
Treatment on discharge	EMB, ETH, RMP, PZA	RMP, ETH, EMB, PZA	RMP, INH, EMB, terizidone	AMK, OFX and ETH	RMP, EMB and PZA
CTCAE grading of most severe reaction	Peripheral neuropathy Grade 3	Peripheral neuropathy Grade 3	Oedema Grade 2	Hepatitis Grade 3	SJS/TEN overlap Grade 4

*Combination tablet of RMP, INH, ETH and EMB.
MDH = multiple drug hypersensitivity; INH = isoniazid; RMP = rifampicin; TB = tuberculosis; CADR = cutaneous adverse drug reaction; DHS = drug hypersensitivity syndrome; SJS = Stevens Johnson syndrome; TEN = toxic epidermal necrolysis; OFX = ofloxacin; ETH = ethionamide; SM = streptomycin; AMK = amikacin; CMV = cytomegalovirus; PZA = pyrazinamide; CTCAE = common terminology criteria for adverse events.

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52 . *what percentage  had mdhs

53 . tab mdhs
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mdhs	Freq.	Percent	Cum.
No	63	64.29	64.29
Yes	35	35.71	100.00
Total	98	100.00	

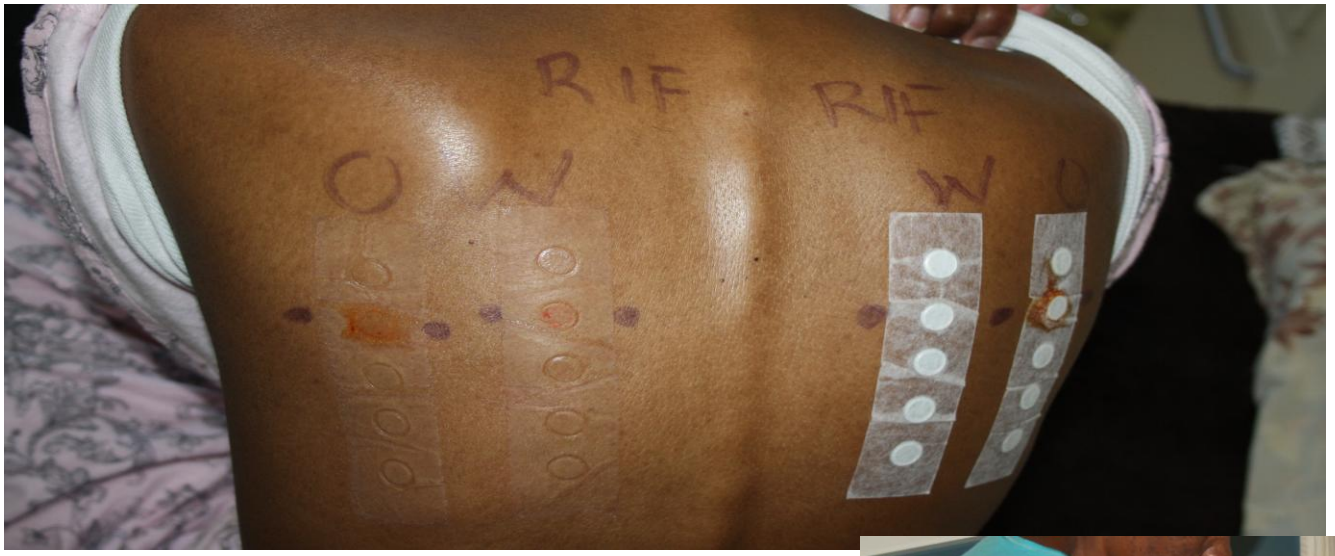
- The most commonly implicated 2nd line drugs are fluoroquinolones (ofloxacin or moxifloxacin), streptomycin and ethionamide.
- Kanamycin also induced reactions, but <<< frequently

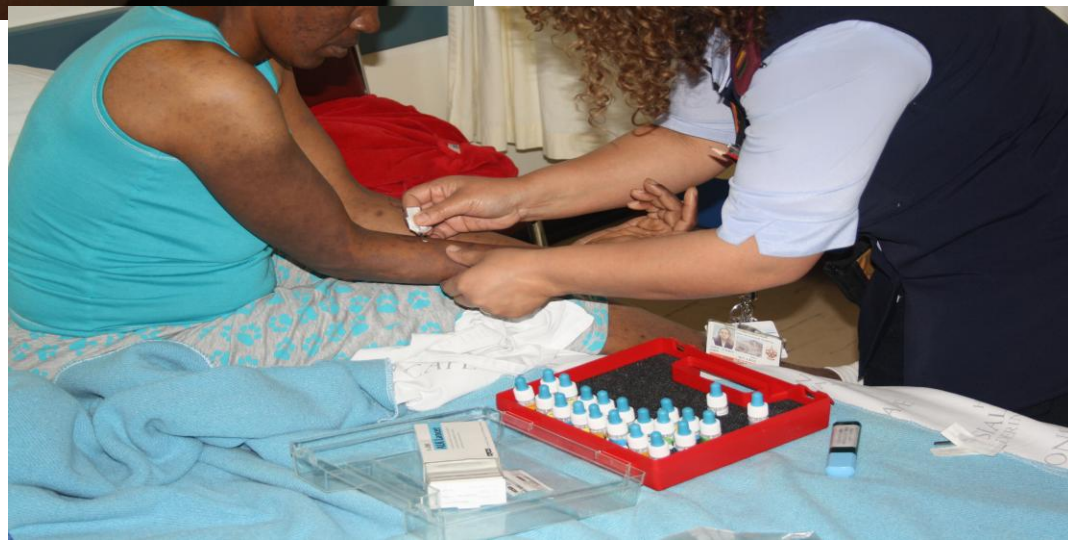
Hypotheses

- Non-specific immune dysfunctional and dysregulated immune responses in HIV
- Rechallenging too soon after CADR during – recommendation ranges from 6 weeks to 6 months

- The excessive immune responses confirmed with patch testing and skin prick testing in the same cohort
- Rechallenges reactions in HIV-infected participants characterized by systemic rather than localized reactions

Lehloenya RJ, Todd G, Wallace J, Ngwanya MR, Muloiwa R, Dheda K Br J Dermatol 2016


RIF
RIF



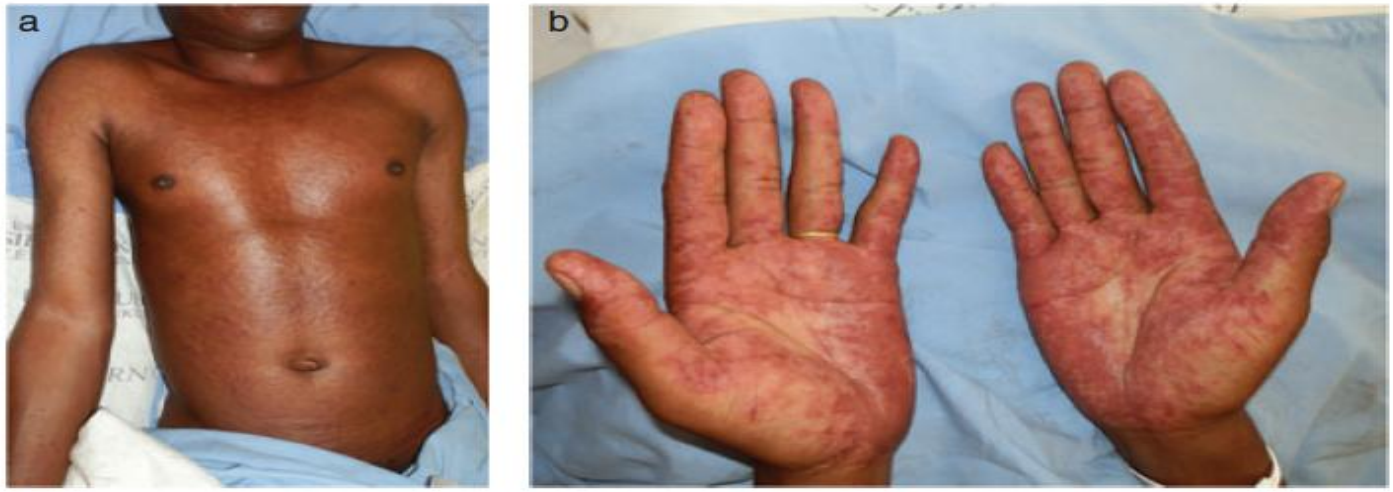


Fig. 1. (a) Monomorphous folliculocentric papules on a background of erythema extending beyond the area of the patch test, which was performed on the back. (b) Palmar erythema with areas of focal necrosis.

Shebe K, Ngwanya MR, Gantsho N, Lehloenya RJ. Contact Dermatitis. 2014 Feb;70(2):125-7

Message

A third of patients will develop a clinically significant ADR on exposure to a TB drug they have not previously encountered

The implicated 2nd line drugs are fluoroquinolones (ofloxacin or moxifloxacin), streptomycin and ethionamide

95% of these occur within 10 days

Rechallenge with first-line drugs

IS THE STRAIN(S) OF TB SENSITIVE TO THE DRUGS YOU ARE GOING TO RE-EXPOSE THE PATIENT TO?

CONFIRM DURATION OF Rx (if already on the continuation phase, no need for PZA & EMB)

The drugs should be rechallenged sequentially and additively

Sequence of rechallenge

- The order the drugs are rechallenged based on the knowledge that, of the 4 first line agents, INH has the highest early bactericidal activity followed respectively RIF, PZA and lastly EMB.

- We hypothesize that this sequence is the most likely to minimize development of drug resistance and offer the best mycobacterial suppression during the potentially prolonged rechallenge process.

Jindani A, Doré C, Mitchison DA. Bactericidal and sterilizing activities of antituberculosis drugs during thefirst 14 days. Am J Respir Crit Care Med 2003;167:1348–1354.
Donald PR, Diacon AH. The early bactericidal activity of anti-tuberculosis drugs: a literature review.Tuberculosis (Edinb). 2008 Aug;88 Suppl 1:S75-83

Current cohort of 98 patients

Confirmed rechallenge reactions

Offending drug
RIF (n=21)
INH (n=23)
PZA (n= 19)
EMB (n=16)

Message

- All 4 first line drugs cause significant proportion of both forms SJS/TEN and DRESS
- The assumption absolving EMB is wrong and dangerous

Features of a rechallenge reaction

- Itch, hepatitis and fever were the most frequent reactions in 23 patients occurring in 48, 39 and 35% of the patients respectively

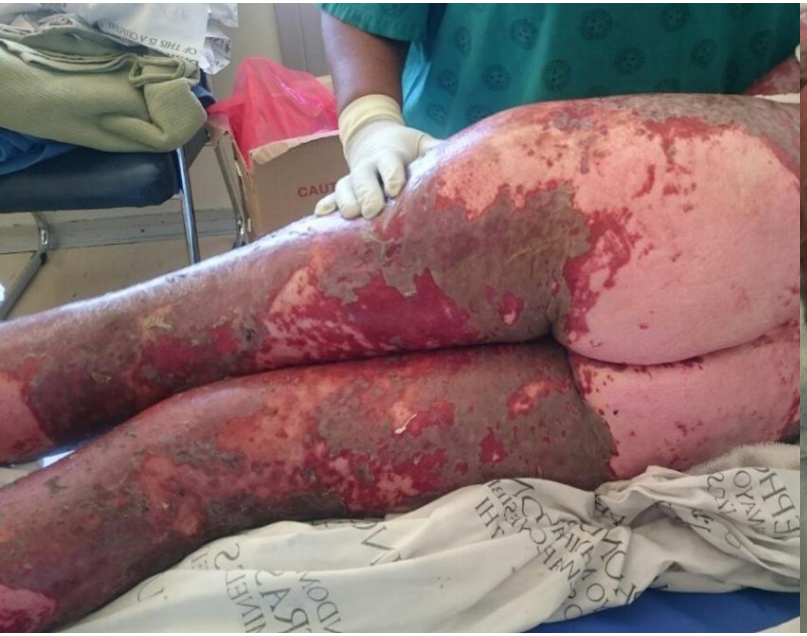
Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. Int J Tuberc Lung Dis. 2011;15(12):1649-57

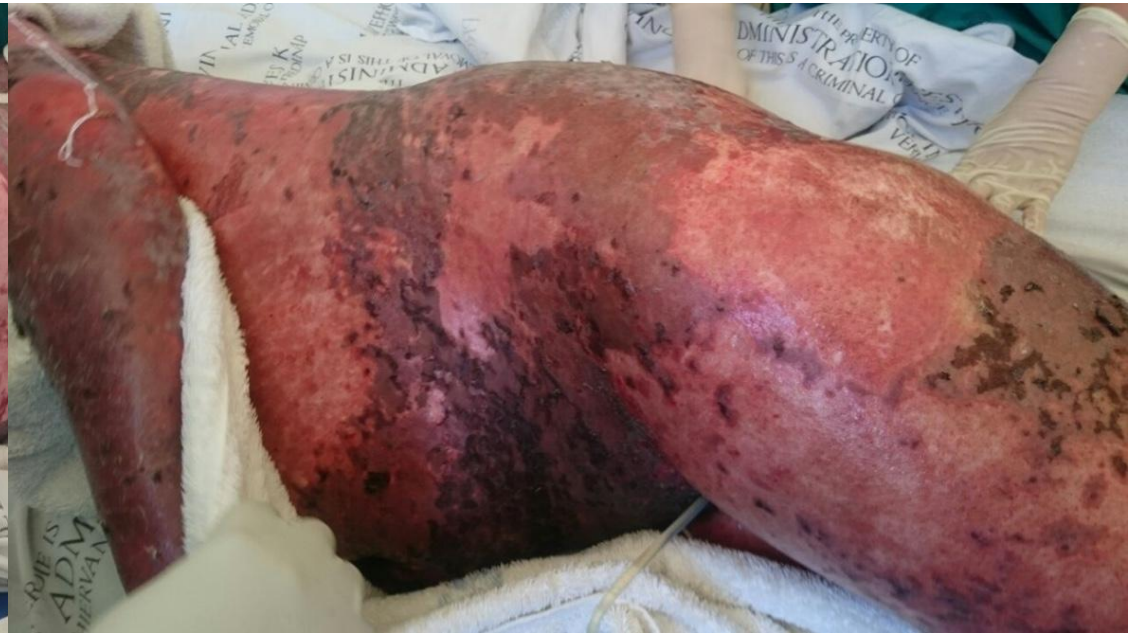
- In our cohort of 98 patients, the commonest features were erythematous followed by hepatitis itch, eosinophilia, fever and oedema in that order

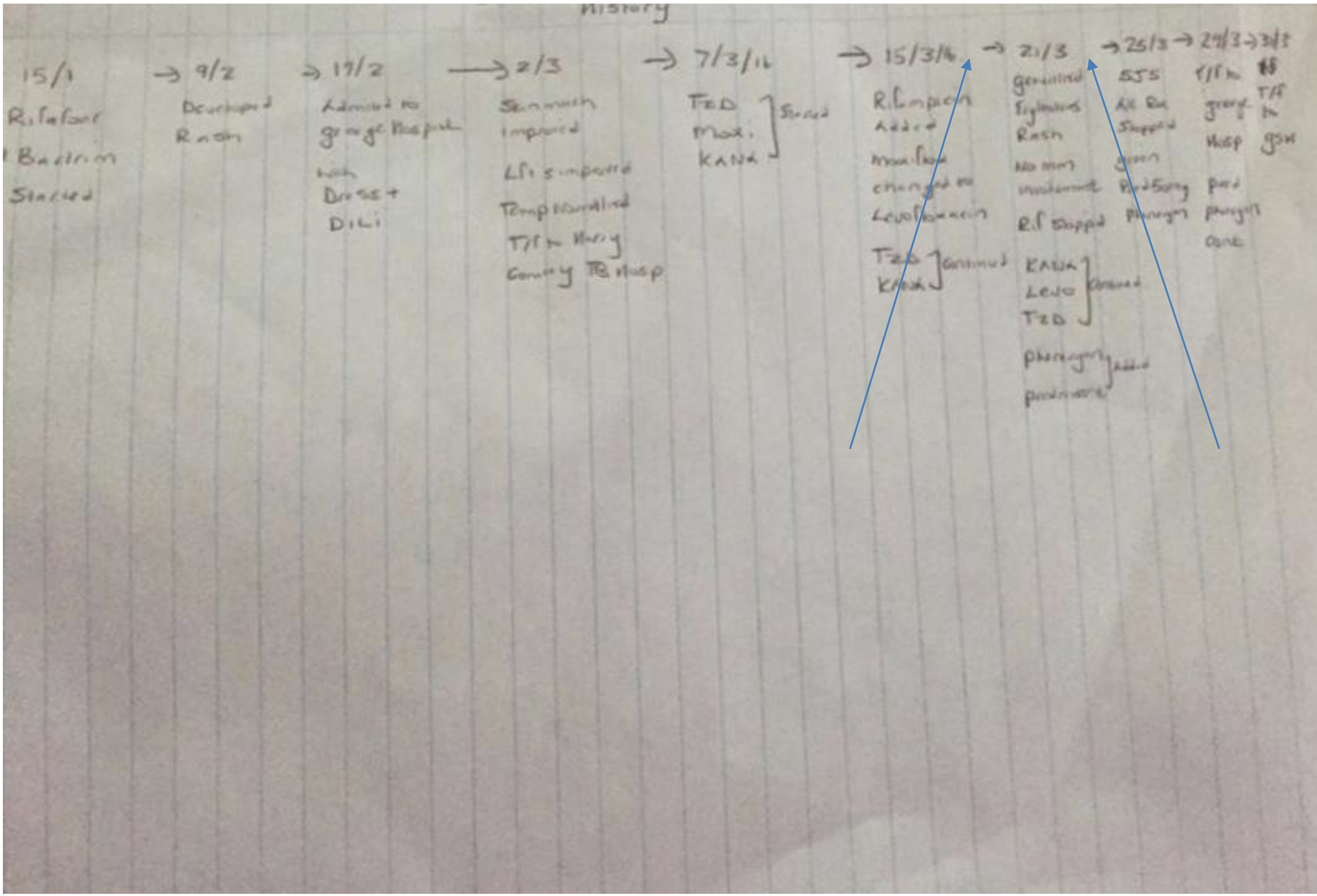
Table 2 Breakdown of the type of re-introduction reactions in 23 patients who were re-challenged with anti-tuberculosis drugs

Feature	Total number of incidents* (n = 23) n (%)
Itch	11 (48)
Hepatitis	9 (39)
Fever	8 (35)
Erythema	4 (17)
Nausea	3 (13)
Vomiting	3 (13)
Oedema	3 (13)
Rigours	2 (9)
Abdominal pain	2 (9)
Headache	1 (4)
Dizziness	1 (4)
Renal impairment	1 (4)
Leucopenia	1 (4)
Thrombocytopenia	1 (4)
Eosinophilia	1 (4)
Myalgia	1 (4)
Tachycardia	1 (4)
Pain	1 (4)
Diarrhoea	1 (4)
Total	55

*Some patients presented with more than one feature. There were a mean of 2.4 (1–7) incidents per reaction.






History
15/1
Bactrim
Started
9/2
Developed
Rash
19/2
Admitted to
with
DILI
2/3
improved
Temp Normalised
TB Hosp
7/3/16
TZD
Mox.
KANA
Started
15/3/16
Added
changed to
Levofloxacin
TZD
KANA
Continued
21/3
Rash
Rif Stopped
KANA
Levo
TZD
Added
25/3
SJS
All Rx
Stopped
29/3
3/3

Lesson

- IF YOU ARE GOING TO RECHALLENGE KNOW FEATURES OF A RECHALLENGE REACTION
- HAVE ACCESS TO THOSE “FEATURES”
- EARLY WITHDRAWAL OF THE OFFENDING DRUG SAVES LIVES

Intervals between new drugs

- In 22/23 patients, the rechallenge reactions occurred within 72 h of exposure to the offending drug

Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. Int J Tuberc Lung Dis. 2011;15(12):1649-57

- Similar finding in our current cohort

Message

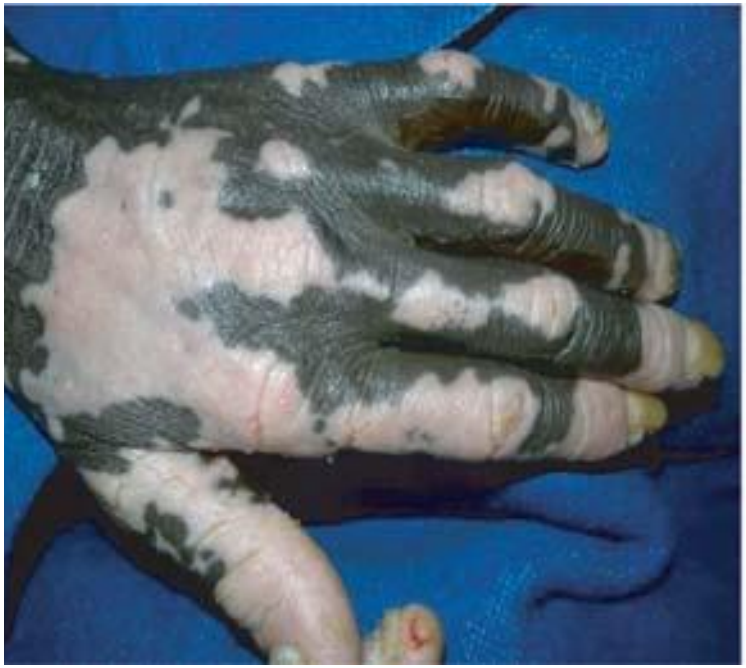
- REINTRODUCE A NEW DRUG AT LEAST AT 4 DAY INTERVALS
- ON THE PROVISO THERE IS NO RECHALLENGE REACTION

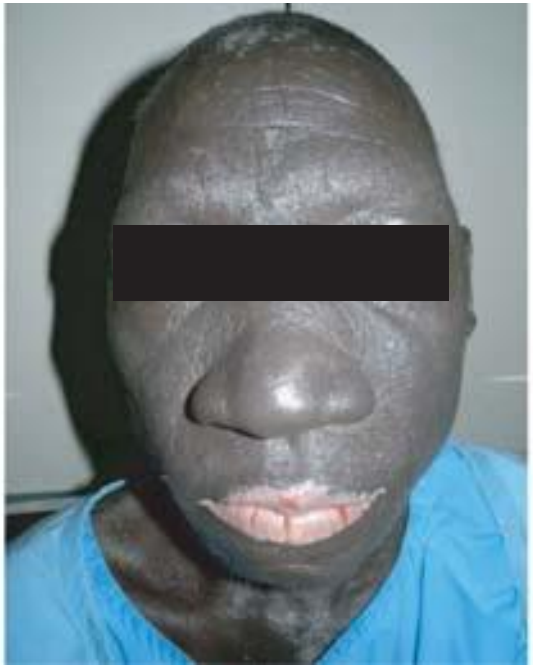
J Antimicrob Chemother 2012
doi:10.1093/jac/dks225
Advance Access publication 11 June 2012

Lichenoid drug reaction to antituberculosis drugs treated through with topical steroids and phototherapy

Rannakoe J. Lehloenya[1,2]*, Gail Todd[1], Lesiba Mogotlane[3], Nomphelo Gantsho[1], Carol Hlela[1,4] and Keertan Dheda[2,4]

(b) (c)





ıoid drug reaction showing depigmentation, hyperpigmentation and fissuring. (c) Clinicall
ș therapy.

Lehloenya RJ, Kgokolo M. Dermatol Clin. 2014 Apr;32(2):227-35

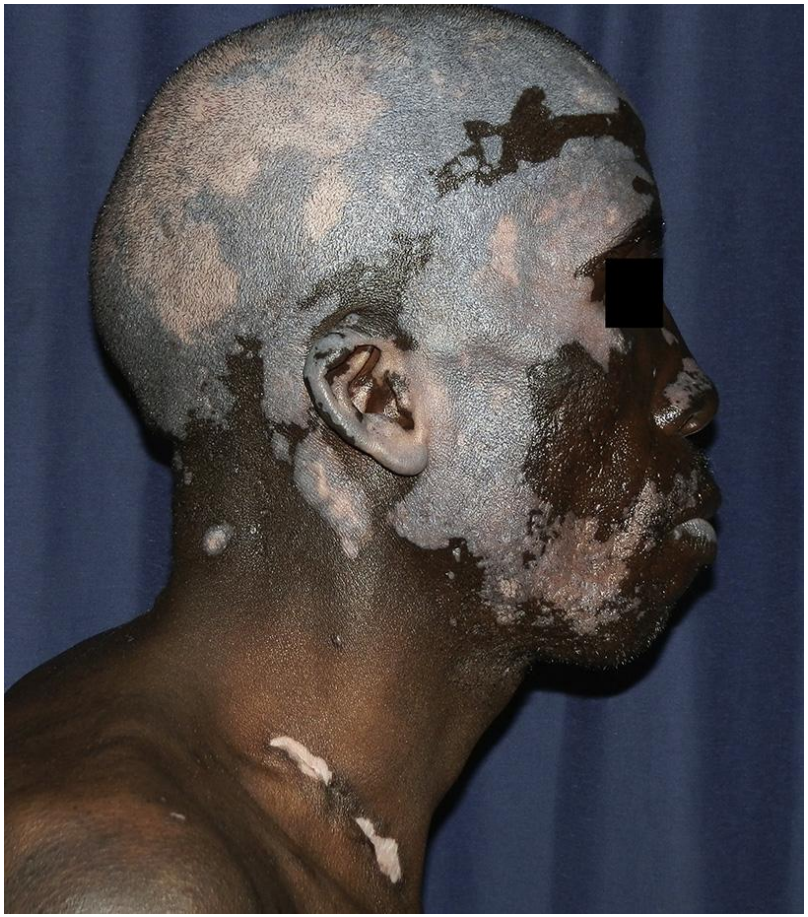


Fig. 5. Lichenoid drug eruption with depigmentation in an HIV-infected man on treatment of a second episode of tuberculosis with Rifafour, a combination drug of rifampicin, isoniazid, pyrazinamide, and ethambutol. The rash initially developed during the first course of tuberculosis treatment and resulted in areas of depigmentation and hyperpigmentation. This picture shows recurrence with violaceous patches within the depigmented areas from the first episode.

Angioedema

- Desensitization is possible but this is highly specialized

I am always happy to advise but I need a complete history always preferably copies of prescription charts and notes

rannakoe.lehloenya@uct.ac.za

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- Most importantly my Patients