Long-term HIV and tuberculosis outcomes in co-infected patients with treatment-limiting severe cutaneous adverse reactions

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Declaration

I, SIMON HANS VEENSTRA, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. No part of this work has 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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Format and Contributions

This thesis is presented in the Published/Publication-ready format. The findings of this manuscript with the title, "Long-term HIV and tuberculosis outcomes in co-infected patients with treatment-limiting severe cutaneous adverse reactions" will be submitted to the International Journal of Tuberculosis and Lung Disease for review for publication.

The data from this study was collected from the IMARI-SA registry and biorepository.
JP and RL conceptualised the work. SV, NP, MNP, JW and MAP were involved in data acquisition. SV, BNT, MNP analysed the data and SV wrote the manuscript under the guidance of JP and MNP. All authors critically reviewed, read, and commented on the final draft. JP, RL, SD, EP and GM gave the final approval prior to submission to the International Journal of Tuberculosis and Lung Disease.

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LIST OF ABBREVIATIONS

ADR	adverse drug reactions
ART	antiretroviral therapy
BSA	body surface area
DRESS	drug reaction with eosinophilia and systemic symptoms
EPTB	extra-pulmonary tuberculosis
FLTD	first-line tuberculosis drugs
GFBDE	generalised fixed bullous drug eruption
GSH	Groote Schuur Hospital
HIV	human immunodeficiency virus
HREC	Human Research Ethics Committee
IM-ADR	immune-mediated adverse drug reactions
IMARI	Immune-mediated adverse drug reactions Africa study
IQR	interquartile range
LOS	length of stay
NHLS	National Health Laboratory Services
PLWH	people living with HIV
PTB	pulmonary tuberculosis
RH	rifampicin/isoniazid
RHZE	rifampicin/isoniazid/pyrazinamide/ethambutol
SA	South Africa
SCAR	severe cutaneous adverse reactions
SDC	sequential drug challenge
SJS/TEN	Steven-Johnson syndrome/toxic epidermal necrolysis
SPV	Single Patient Viewer
TB	tuberculosis
UCT	University of Cape Town
VL	Viral load

PUBLICATION-READY MANUSCRIPT

LONG-TERM HIV AND TUBERCULOSIS OUTCOMES IN CO-INFECTED PATIENTS WITH TREATMENT-LIMITING SEVERE CUTANEOUS ADVERSE REACTIONS

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Short title: Long-term HIV/TB outcomes in SCAR

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Authors contributions:
JP and RL conceptualised the work. SV, NP, MNP, JW and MAP were involved in data acquisition. SV, BNT, MNP analysed the data and SV wrote the first draft under the guidance of JP and MNP. All authors critically reviewed, read, and contributed to the final draft. JP, RL, SD, EP and GM gave the final approval. The IMARI group must also be acknowledged for their support and ongoing work in this field.

ABSTRACT

Background

Treatment-limiting severe cutaneous adverse reactions (SCAR) occur more commonly amongst persons co-infected with tuberculosis (TB) and advanced HIV. The impact of SCAR on long-term HIV and TB outcomes is unknown.

Methods

Patients with active TB and/or HIV admitted to Groote Schuur Hospital, Cape Town, South Africa with SCAR between 1/10/2018 and 30/09/2021 were eligible. Clinical and laboratory follow-up data was collected for 6 and 12-month outcomes: mortality, TB and antiretroviral therapy (ART) regimen changes, TB treatment completion, and CD4 count recovery.

Results

Forty-eight SCAR admissions included: 34, 11, and 3 HIV-associated TB, HIV-only and TB-only patients with 32, 13 and 3 cases of drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome/toxic epidermal necrolysis and generalised bullous fixed drug eruption respectively. Nine (19%), all HIV-positive, were deceased at 12-months, and 12 (25%) were lost to all care levels. Amongst TB-SCAR patients, seven (21%) were discharged on all four first-line anti-TB drugs (FLTD), while 12 (33%) had discharge regimens with no FLTDs; 24/37 (65%) completed TB treatment. Amongst HIV-SCAR patients, 10/31 (32%) changed ART regimen. If retained in care (24/36), median (IQR) CD4 counts increased by 12-months post-SCAR (115 (62-175) vs. 319 (134-439) cells/uL).

Conclusion

SCAR admission amongst patients with HIV-associated TB results in substantial mortality, and considerable treatment complexity. However, if retained in care, TB regimens are successfully completed, and immune recovery is good despite SCAR.

South Africa (SA) has one of the highest burdens of tuberculosis (TB) globally and coinfection with human immunodeficiency virus (HIV) exceeds 50%[1]. The management of HIV-associated TB poses several clinical challenges including drug-drug interactions, polypharmacy, and adverse drug reactions (ADR)[2]. In HIV/TB endemic settings severe immune-mediated ADR (IM-ADR) such as severe cutaneous adverse reactions (SCAR) and drug-induced liver injury, occur more commonly amongst persons with HIV-associated TB than those with TB alone, with IM-ADR occurring 2-100-fold more commonly in persons living with HIV (PLWH)[3–5]. Treatment-limiting, life-threatening SCAR secondary to first-line anti-TB drugs (FLTD), cotrimoxazole and antiretrovirals account for many hospitalisations, resulting in considerable morbidity, prolonged hospitalisation, and healthcare expenditure[6]. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome are the common SCAR phenotypes[4,6,7].

TB treatment completion and cure rates approach 80% in HIV-associated TB patients in SA[8,9]. However, there is limited data on long-term TB outcomes in FLTD-associated SCAR. Our unit has pioneered sequential drug challenge (SDC) to assist in rapid re-initiation of all non-culprit FLTD in TB-SCAR[10] yet, despite 88% of TB-SCAR patients undergoing SDC, only half remain on at least one FLTD[6] and their treatment completion rates are unknown. SA has the largest antiretroviral therapy (ART) program in the world, with more than 60% of PLWH on ART and around 90% having sustained virological suppression[11,12]. There is no data on the short- and long-term impact of SCAR on ART and CD4 count recovery, and given data showing increased interruption of care following in-hospital ART commencement, there is potential concern[13,14]. The aim of this study was to describe the 6 and 12-month HIV and TB outcomes amongst patients hospitalised for HIV/TB-associated SCAR. This included CD4 counts, viral load (VL), retention in care, ART regimen changes and TB completion and cure rates, TB regimen changes and mortality.

METHODS

Patient selection and ethical approval

Patients with SCAR admitted to the dermatology ward of Groote Schuur Hospital (GSH), a tertiary level hospital, in Cape Town, Western Cape, South Africa were reviewed for inclusion into this study. In 2021, the Cape Town metropole had an estimated population of 4.78 million people of which GSH serves approximately half[15]. At a provincial level, the estimated TB burden is one of the highest in the country[16]. This retrospective cohort study reviewed patients that had been prospectively enrolled in the Immune-mediated adverse drug reactions (IMARI) Africa study (University of Cape Town (UCT) Human Research Ethics Committee (HREC) ref. no: R031/2018). SCAR patients were eligible for inclusion in this study if they met the following criteria: i) 12 years or older, ii) either HIV-positive, active TB alone, or HIV-associated TB, iii) hospitalised due to SCAR necessitating treatment interruptions, iv) had a validated (possible, probable, or definite) SCAR phenotype of DRESS,

SJS/TEN, or generalised bullous fixed drug eruption (GBFDE), and v) provided consent for collection of their clinical data. The study and 12-month follow-up period spanned three years from 1st October 2018 to 30th September 2021. All patients had baseline data, phenotype validation and drug causality assessment performed as part of the IMARI Africa study. IMARI uses RegiSCAR[17,18] phenotype validation for SJS/TEN and DRESS, and Naranjo and/or Alden scoring tools for drug causality assessment[19,20]. GBFDE was diagnosed by a Dermatologist. The study was approved by the UCT HREC, Faculty of Health Sciences (HREC: 577/2021).

Data collection, definitions, and analysis

Baseline TB, HIV and SCAR admission data was collected retrospectively through the IMARI registry. Baseline variables included: demographics and medical history; details of previous and current TB (including site-of-disease, method of diagnosis and starting treatment regimen); HIV details pre-admission (including date of diagnosis, CD4 count, viral load (VL) and ART); and SCAR admission variables (including onset of reaction, clinical and laboratory markers of phenotype and severity, hospital length of stay (LOS), and SDC outcomes). Table 1 documents these outcome measures and defintions. Long-term TB and HIV outcomes were collected retrospectively at 6- and 12-month time-points after the date of discharge from SCAR hospitalisation. Virological suppression was defined as <400 copies/ml. To minimise missing data, several methods were used to collect outcome data including: folder and drug allergy clinic record review, visit-tracking on the Clinicom hospital booking system, and the provincial Single Patient Viewer (SPV). Clinicom and SPV are electronic medical record systems tracking all patient encounters across various levels of the healthcare service in the Western Cape province. Additionally, SPV captures drug dispensing and laboratory information. The National Health Laboratory Services (NHLS) electronic results platform was searched for all HIV/TB laboratory testing performed at all levels of care during the 12-month follow-up period. Figure 1A describes TB and HIV outcome definitions used, and the window period allowed around 6- and 12-month time-points for key outcome variables. Loss-to-follow-up (LTFU) was defined as no medical encounter or pick-up of medication for three consecutive months. All data was stored on a password protected electronic database (REDCap 12.0.19 - © 2022 Vanderbilt University), and de-identified data was exported for analysis on Microsoft Excel, version 16.54 (Microsoft Corporation ©, 2021) and STATA, version 15.1 (StataCorp. 2017. College Station, TX: StataCorp LLC.). All predictor variables with a p-value < 0.2 in univariable logistic regression models were used to build multivariable logistic regression models using a forward stepwise method at 0.05 level of significance. A variable that did not improve the model fit was dropped.

RESULTS

Baseline Characteristics and Clinical Information

Table 2 provides the baseline characteristics, and TB and HIV disease details for the cohort of 48 validated HIV or TB-associated SCAR patients, and Figure1B. illustrates the stratification by phenotype (32 DRESS, 13 SJS/TEN and 3 GBFDE) and HIV/TB status (34 HIV-associated TB, 3 TB-only and 11 HIV-only). The median (IQR) age was 38 (30-45) years, and 60% were female. Six patients had a history of previous TB with exposure to FLTD without documented SCAR (three were diagnosed with HIV concurrently, one soon after TB diagnosis and one diagnosed at an unknown timepoint). On admission, 37 (77%) participants were on anti-TB treatment, and all except one, were receiving FLTDs. TB was confirmed in 24/37 (65%) SCAR admissions, either by GeneXpert PCR (GXP) alone (n=19, 79%), culture alone (n=3, 13%), or both (n=2, 8%); all 24 confirmed TB cases were rifampicin-sensitive (one patient among them INH monoresistant). The remainder (n=13) had been started empirically on TB treatment based on clinical symptoms and suggestive imaging. Baseline TB characteristics were similar in people with HIV-associated TB compared to the overall cohort, except that all HIV-negative TB patients (n=3) had pulmonary TB (PTB) alone while extrapulmonary TB (EPTB) occurred in 19/34 (56%) of HIV-associated TB patients. Median (IQR) CD4 cell count was lower amongst people with HIV-associated TB compared with HIV-positive alone [90 (61-142) vs 269(134-391) cells/uL; P = .162)].

Overall, 45 (94%) participants had a diagnosis of HIV, 44 had baseline CD4 cell counts around time of SCAR, with a median (IQR) baseline CD4 cell count of 115 (62-175) cells/uL. Baseline VL results were only available for 15/45 (33%) within the six months pre- and three months post-SCAR, but it is notable that of the seven VLs available pre-SCAR only one had virological suppression. Nine patients had VL performed (one participant had a repeat VL) in the three months following SCAR and virological suppression was noted in three participants. Pre-admission ART was documented for 31/45 (69%), with 26/31 (84%) on SA guideline specified first-line ART and 5/31 (16%) on second-line ART[21]. Cotrimoxazole prophylaxis had been prescribed for 29/34 (85%) of patients with CD4 cell count <200cells/uL.

SCAR phenotypes and offending drugs

Supplementary Table 1 provides details of the RegiSCAR probability and clinical characteristics of the admission SCAR by phenotype. DRESS was the commonest phenotype occurring in 32/48 (67%). No significant differences in demographics or TB and HIV baseline characteristics were noted between SCAR phenotypes as shown in Table 2. Amongst DRESS cases, 23/32 (72%) were definite or probable, while 10/13 (77%) of SJS/TEN cases were definite or probable. Eight of 13 cases had >30% body surface area (BSA) involvement and were designated TEN. The median (IQR) length of hospital stay (LOS) was 26 (11-47) days for all SCAR and similar across all phenotypes. Supplementary Table 2 provides details of suspected drugs with the highest Naranjo scores, and the outcomes of SDC. SDC to

FLTD treatment was performed in 30/37 (81%) TB-SCAR; two patients died prior to SDC, one had their TB diagnosis refuted, three went straight onto a modified regimen due to severity of organ involvement, and one did not undergo SDC for unknown reasons. There were 17 TB-SCAR patients with a positive reaction to ≥1 FLTD, with ten reacting to a single TB drug and seven to more than one FLTD.

Long-term TB and HIV outcomes

At 12-months, 9/48 (19%) of SCAR patients had died; all were HIV-positive and eight had TB. An exploratory logistic regression analysis presented in supplementary table 3 showed no clear predictors of mortality. A further 12/48 (25%) were not connected with any level of provincial health care services. Of the eight co-infected patients who died, five (63%) had EPTB vs 14/34 (41%) among those who survived. Those that died had both higher median (IQR) BSA involvement [75% (50-80%) vs 56% (50-70%); *P = .171*)] and lower median (IQR) baseline CD4 count [72 (62-118) cells/uL vs 109 (53-200) cells/uL; *P = .305*] compared to those with SCAR that survived, but neither of these differences reached statistical significance. Median (IQR) peak eosinophil was also non-significantly higher in those who died [3.14 x10^9/L (2.22-4.05 x10^9/L) vs 1.05 x10^9/L (0.6-2.34 x10^9/L); *P = .49]*.

Table 3 details the impact of SCAR on TB and HIV treatment and outcomes. Thirty-four TB-SCAR patients were discharged with anti-tuberculosis regimens including: eight rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) (seven pre-admission FLTD, and one with rifabutin substituted in for rifampicin), five on continuation-phase (rifampicin/isoniazid (RH)), nine modified regimens with at least one FLTD, 12 second-line regimen with no FLTD. All patients with modified regimens had >6 months of therapy, and at 12-months 20/37(54%) had completed treatment with 4/37(11%) having evidence of bacteriological cure. One participant was retreated for recurrent TB after their initial TB-SCAR and tolerated FLTD (see footnote in Table 2). Of the eight with TB that died, only one patient was discharged on a full FLTD regimen (RHZE) and only 3 (37.5%) had any FLTD included in their discharge regimen.

Of the 45 HIV-SCAR cases, 38 (84%) were on ART at the time of discharge, of which 10 patients commenced first-line ART in hospital. Thirty-six PLWH were alive at 12-months post-SCAR, 24 (67%) were still collecting ART, while 12 (33%) were no longer in HIV care. Of the 31 PLWH who were on ART pre-SCAR, regimens were changed in 10 (32%), four to new dolutegravir-based fixed dose combinations, four due to a SCAR culprit drug in theinitial ART regimen (two nevirapine, one tenofovir/efavirenz combination and one dolutegravir). PLWH that were retained in care post-SCAR admission showed increases in median (IQR) CD4 counts at 6- and 12-months (Figure 2) [Baseline: 115 (62-175) cells/uL vs. 6-months: 199 (89-427) cells/uL vs. 12-months: 319 (134-439) cells/uL]. At 12-months, CD4 cell count recovery was less in SJS/TEN-SCAR compared to DRESS-SCAR cases [183 (65-313) cells/uL vs 388 (314-605) cells/uL]. VL data was only available for 15/36(42%) of HIV-

SCAR cases at 12-months post-SCAR, and 12/15 (80%) showed virological suppression, with no differences between SCAR phenotypes.

DISCUSSION

Our study reports 6- and 12-month outcomes for the largest cohort of HIV and TB-associated SCAR reported to date, with more than two-thirds of patients with HIV-associated TB. Our major findings include: i) one fifth of patients died, most commonly in the first three months post-SCAR, ii) the majority of TB regimens require modification of one or more drug, but despite altered and prolonged therapy 65% of patients have successful TB outcomes, iii) nearly one third of ART regimens are changed post-SCAR, and iv) if HIV-positive SCAR patients are retained in care, 6- and 12- month immune recovery can be expected.

People with HIV-associated TB admitted with SCAR had advanced immunosuppression, with a median CD4 cell count of 90 cells/uL. TB remains the leading cause of death in PLWH in SA and patients with a CD4 cell count <100 cells/uL have reported 6- and 12-month mortality of 6-25% [22,23]. Thus, although the mortality rate of 19% in our cohort is high, and indicates the profound vulnerability of this patient population, it does not appear that SCAR admission by itself significantly increased mortality. This is consistent with our findings in a related cohort of only SJS/TEN-SCAR and a review of mortality in DRESS syndrome, where the mortality rate was 3%. This is consistent with the lower end of the mortality scale of DRESS in HIV/TB uninfected individuals in the developed world[24,25]. Several factors may be driving this lower-than-expected SCAR mortality amongst people with HIV-associated TB compared to other SCAR cohorts, including the younger population with less co-morbid organ dysfunction, and differences in immune-responses to specific drugs e.g. FLTD versus allopurinol [24]. However, it is noted that due to the high number of people no longer in clinical care at 12-months, we are cautious in drawing conclusions regarding mortality and predictors of mortality.

TB-SCAR necessitated alteration and lengthening of TB treatment regimens in 80% of patients. Our unit has pioneered SDC to ensure that TB-SCAR patients, especially those with co-morbid HIV, are re-established timeously on as many FLTDs as possible[10], and in this cohort nearly two fifths of TB-SCAR patients had at least two FLTDs included in their regimens after SCAR and seven patients recommenced all four FLTDs. These findings support efforts to incorporate SDC for SCAR into national policy in high HIV/TB burden settings. Despite considerable modification of TB regimens, 65% of SCAR patients had successful treatment outcomes. These outcomes are lower than SA studies that report TB treatment outcomes among TB patients in general (combined treatment completion and cure rates) which range from 70%-82% and fall significantly short of the World Health Organization goal of 85%[22,26–28].

HIV-care was also disrupted by SCAR admission, with one in five changing ART regimen within the 12-months post-SCAR. In addition, we could not find any record of HIV care or ART for 12

of our post-SCAR patients, which may reflect death, movement out of the province, or ART interruption. However, if HIV patients were retained in care, immune recovery, as measured by CD4 cell count, progressively improved in the 12-months post-SCAR. There was a slower CD4 count improvement over the first 6-months compared to national expected rates [199 (89-427) cells/uL vs. 315 (198-463) cells/uL], which may have several contributing factors including: interruption or delayed initiation of ART; lower baseline CD4 count, and even potentially direct immunological effects of SCAR[29,30]. However, these effects appeared to wane as 12-month CD4 cell counts were similar to the national average (median 319 vs. 358 cells/uL)

This study has important limitations. Despite attempts at telephonic contact and home visits, for certain patients the linkage to ART and TB care services was reliant on the single patient viewer recording electronic clinical encounters and medication dispensing. Thus, we were unable to determine if patients were accessing care in other provinces, and we need to assume that dispensed medication equates to treatment adherence. In addition, data capturing in some clinics may be incomplete accounting for some of the missing data. In most cases, CD4 cell count data supports ART adherence, and the integrated coverage of the single patient viewer is well established[31]. The observational nature of this study and reliance on routine clinical care meant that there was missing data, particular for VL, which are not regularly measured in primary care. For certain sub-group analyses, sample size within the cohort was too small to make robust conclusions. Therefore, we have been cautious in some of our conclusions.

Our study is the largest of its kind following HIV, TB and HIV-associated TB individuals post-SCAR and it demonstrates the complexity created by SCAR amongst this vulnerable population. It also demonstrates the profound impact of SCAR on HIV and TB treatment. Mortality, although high, was similar to other non-SCAR HIV/TB cohorts demonstrating that the acute management and SDC strategy used may have optimised these patients' outcomes. However, we feel there remains a need to support ongoing research to improve prevention and treatment of SCAR amongst PLWH [32,33]. In addition, prospective registry-related follow-ups and clinical review may help to further improve both the short- and long-term outcomes and understanding of the natural history in these complex patients.

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TABLES AND FIGURES

Table 1. Long-term HIV and TB outcomes and measures.

	Long term outcome(s)	Measures	Timeframe from IM-ADR
TB	• TB treatment non-compliance • Sputum culture conversion • TB recurrence rates • Altered anti-TB multiple drug regimens • Prolonged treatment interruption • Drug resistance	WHO treatment outcome definitions of treatment completed, interrupted (>2 months), or cured; sputum conversion, recurrence rate. Drug resistance rates (via either culture or NAAT)	0, 6 and 12 months. Sputum conversion at 2 and 5 months. Recurrent disease within 2 years.
HIV	• Viral control • CD4 cell count recovery/immune reconstitution • ART drug resistance	Viral load (aligned to SA National programme) CD4 count Switch to 2nd or 3rd line ART	0 and 12 months 0, 12 and 24 months Switch to 2nd line ART within 2 years

Table 1. Long-term HIV and TB outcomes and measures. This table documents the long-term outcomes in the HIV and TB cohorts with the measures used to gauge these outcomes. ART, anti-retroviral therapy; HIV, human immunodeficiency virus; IM-ADR, immune-mediated adverse drug reaction; NAAT, nucleic acid amplification test; SA, South Africa; TB, tuberculosis; WHO, World Health Organisation

Table 2. Baseline clinical characteristics according to HIV/TB status and SCAR phenotype.

	Overall	HIV-associated TB	DRESS	SJS/TEN	GBFDE
(n, %)	48	34 (71%)	32 (67%)	13 (27%)	3 (6%)
Age (median, IQR)	38 (29.75 – 45.00)	38 (30 – 44.75)	38 (30 - 44)	33 (26 – 48)	40 (38.5 - 48)
Female (n, %)	29 (60%)	19 (56%)	21 (66%)	7 (54%)	1 (33%)
HIV					
HIV infected (n, %)	45 (94%)	34 (100%)	30 (94%)	12 (92%)	3 (100%)
CD4 cells/uL (median (IQR)	115 (62 – 175)	90 (61- 142)	121 (68 - 176)	63 (43 – 116)	336 (178 - 372)
On ART at time of SCAR admission (n, %)	31 (69%)	20 (59%)	17 (57%)	11 (91%)	3 (100%)
FLART (n, %)	26 (84%)	16(80%)	14 (82%)	10 (92%)	2 (67%)
Non-FLART	5 (16%)	4 (20%)	3 (18%)	1 (8%)	1 (33%)
On cotrimoxazole prophylaxis at time of SCAR admission (n, %)	29 (64%)	23 (68%)	15 (50%)	11 (92%)	3 (100%)
TB					
TB (n, %)	37 (77%)	34 (100%)	26 (81%)	9 (69%)	2 (67%)
TB Microbiological confirmation[1]	24/37 (65%)	22/34 (65%)	15/26 (58%)	7/9 (78%)	2 (100%)
Rifampicin sensitive[2]	34/38 (89.5%)	28/30 (93%)	22/24 (92%)	10/10 (100%)	2 (100%)
Location of TB					
PTB alone	18/37 (49%)	15 (44%)	11 (42%)	5 (56%)	2 (100%)
EPTB	19/37 (51%)	19 (56%)	15 (58%)	4 (44%)	0 (0%)
TB regimen on admission					
FLTD regimen	36/37 (97%)	33 (97%)	25 (96%)	9 (100%)	2 (100%)
Previous TB	6 (16%)	5 (15%)	3 (12%)	1 (11%)	2 (100%)
Finished previous TB treatment without SCAR	4 (67%)	3 (60%)	3 (100%)	1 (100%)	0 (0%)

Table 2. Baseline characteristics according to HIV/TB status and SCAR phenotype.

[1]All TB microbiological confirmation was done via GXP PCR except for three that were culture positive alone

[2]One patient was INH monoresistant; the remaining four had no sensitivities available

ART, antiretroviral therapy; GBFDE, generalised bullous fixed drug eruption; DRESS, drug rash with eosinophilia and systemic symptoms; EPTB, extra-pulmonary tuberculosis; FLART, first-line ART; FLTD, first-line anti-tuberculosis drugs; GXP, Gene-Xpert; HIV, human immunodeficiency virus; IQR,

interquartile range; PCR, polymerase chain reaction; PTB, pulmonary tuberculosis; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TB, tuberculosis

Table 3. Key outcomes of patients admitted with FLTD-associated SCAR.

	OVERALL 48	DRESS 32	SJS/TEN 13	GBFDE 3
TB TREATMENT AND OUTCOMES				
TB Discharge regimen (N)	34	25	7	2
RHZE	7/34 (21%)	2/25(8%)	3/7 (43%)	2 (100%)
No-FLTD in regimen	12/34 (35%)	11/25 (44%)	1/7 (14%)	0 (0%)
TB, no SDC	7/37 (19%)	5/32 (16%)	2 (15%)	0 (0%)
not completed SDC due to death	2/7 (29%)	1 (20%)	1 (50%)	0 (0%)
TB diagnosis refuted	1 (14%)	0 (0%)	1 (50%)	0 (0%)
Straight to modified due to organ damage	3 (43%)	3 (60%)	0 (0%)	0 (0%)
Prescribed TB treatment completed	20/34 (59%)	17/25 (68%)	2/7 (29%)	1/2 (50%)
Confirmed Microbiological cure	4/34 (12%)	2/25 (8%)	1/7 (14%)	1/2 (50%)
New TB in 12-months post SCAR[4]	1/48 (2%)	1/32 (3%)	0	0
HIV TREATMENT				
ART started[1]	10/45 (22%)	10/30 (33%)	0 (0%)	0 (0%)
On ART at 12 months[2]	24/36 (67%)	19/29 (66%)	3/8 (38%)	2/3 (66.7%)
Regimen change[3]	10/31 (32%)	6/17 (35%)	4/11 (36%)	0/3 (0%)
SURVIVIAL				
Death at 12 months	9 (19%)	5 (16%)	4 (31%)	0 (0%)
< 3 months	7 (77.8%)	3 (60%)	4 (100%)	0 (0%)
< 6 months	1 (11.1%)	1 (20%)	0 (0%)	0 (0%)
< 12 months	1 (11.1%)	1 (20%)	0 (0%)	0 (0%)

Table 3. Key outcome of patients admitted with FLTD-associated SCAR. Table showing specific TB and HIV outcomes with regards to treatment regimens at discharge, death, TB treatment success rates, and recurrence of TB.

[1]Denominator used is number of HIV positive in each cohort

[2]Denominator used is PLWH alive at 12-months

[3] Denominator used is number of patients on ART pre-SCAR

[4] The one patient who had a recurrence of TB was likely untreated as they were discharged on a backbone regimen of moxifloxacin, terizidone and ethionamide but they never returned for SDC. They subsequently returned with a DRESS syndrome likely secondary to cotrimoxazole and tolerated RHZE on re-initiation.

ART, antiretroviral therapy; DRESS, drug rash with eosinophilia and systemic symptoms; E, ethambutol; FLTD, first-line anti-tuberculosis drugs; GBFDE, generalised bullous fixed drug eruption; H/INH, isoniazid; HIV, human immunodeficiency virus; PLWH, people living with HIV; R, rifampicin; SCAR, severe cutaneous adverse reaction; SDC,

sequential drug challenge; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TB, tuberculosis; Z, pyrazinamide

Figure 1A. Explanations of study period, sampling windows and outcomes.

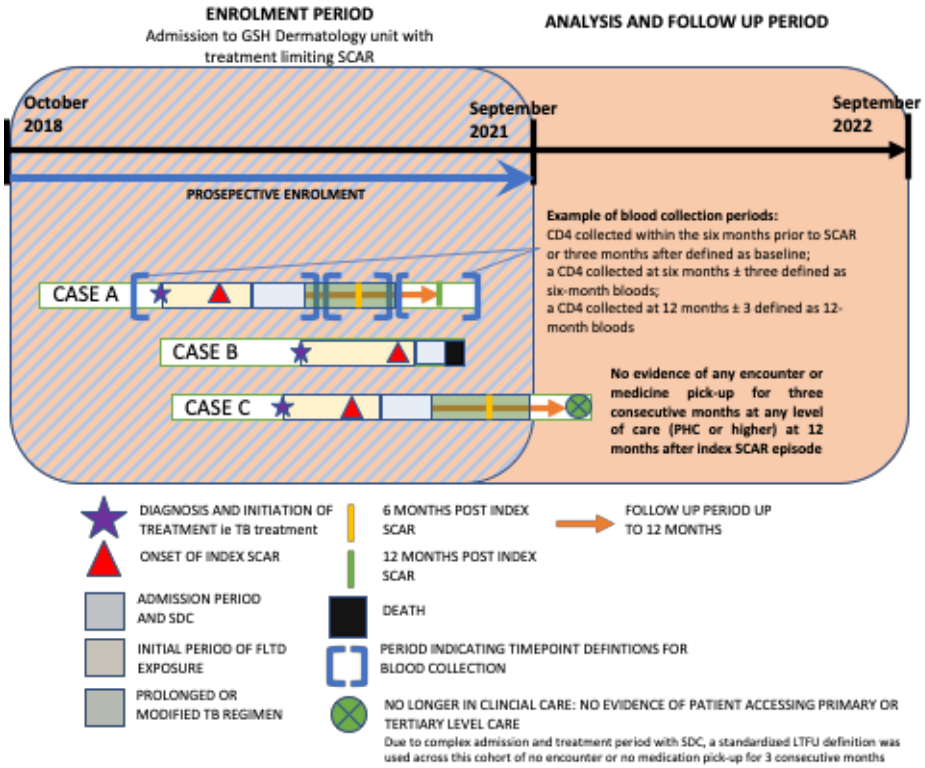


Figure 1A. Explanations of study period, sampling windows and outcomes. The study included prospective cases with different outcomes as the following example cases show: Case A. Admission for FLTD-SCAR with SDC in hospital, prolonged or modified TB treatment and follow-up clinical information available to collect for 6- and 12-months; Case B. Admission for FLTD-SCAR and then dead either during admission or in the 12-month follow up period, and Case C. Admission for FLTD-SCAR with SDC in hospital, prolonged or modified TB treatment and then loss-to-follow-up during the 12-months post-SCAR. FLTD, first-line anti-tuberculosis drugs; GSH, Groote Schuur Hospital; LTFU, loss to follow up; PHC, primary health care; SCAR, severe cutaneous adverse reaction; SDC, sequential drug challenge; TB, tuberculosis

Figure 1B. Flow diagram of included patients.

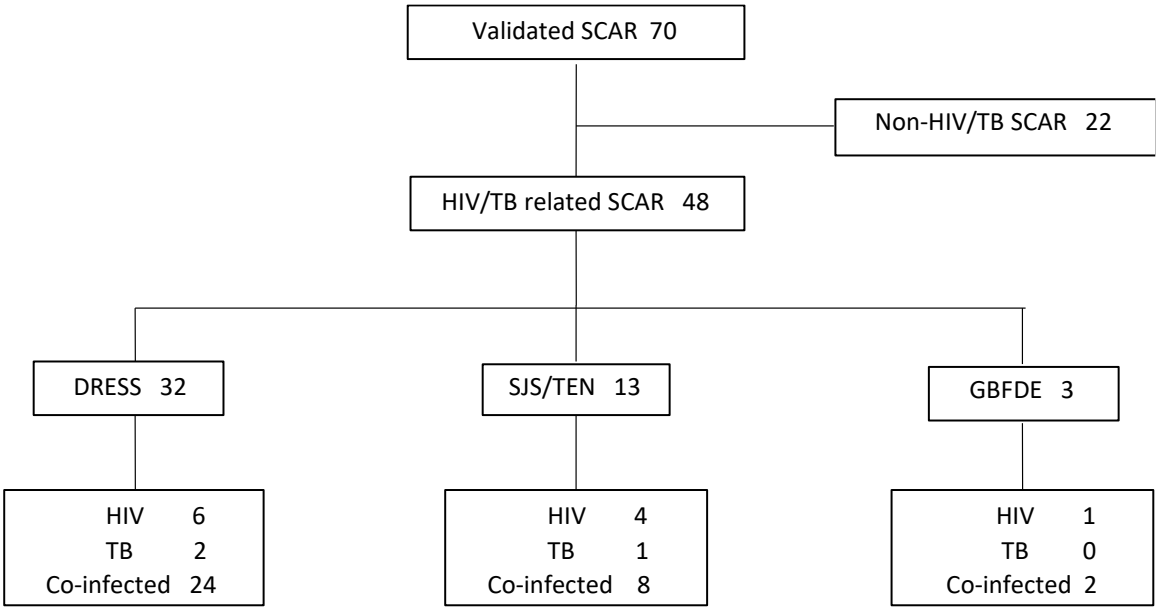
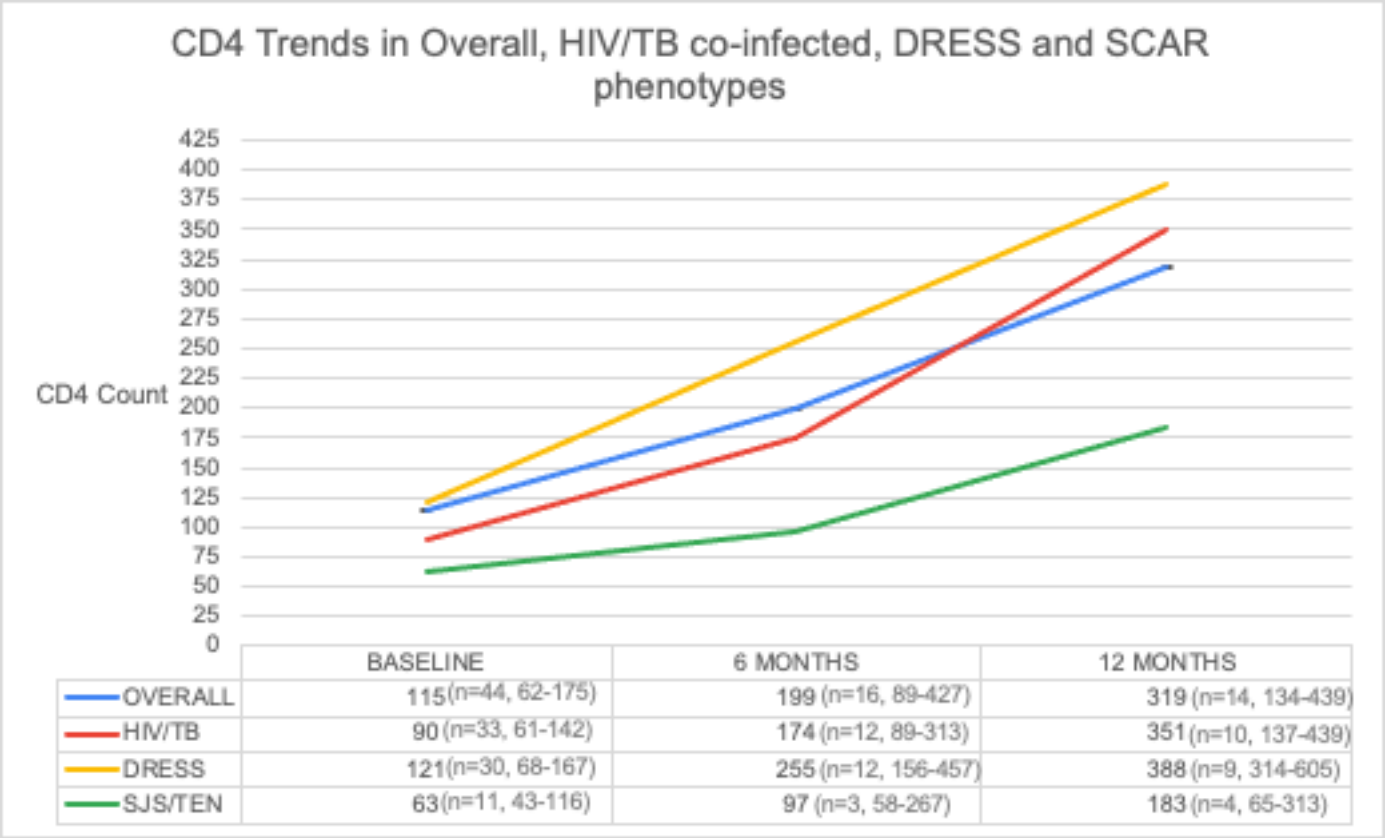


Figure 1B. Flow diagram of included patients. Subclassification by SCAR phenotype with numbers of HIV, TB and co-infected in each SCAR phenotype. SCAR not related to HIV or TB treatment was not included. One patient had missing data and was admitted to another tertiary hospital and was therefore not included. DRESS, drug rash with eosinophilia and systemic symptoms; GBFDE, generalized bullous fixed drug eruption; HIV, human immunodeficiency virus; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/Toxic epidermal necrolysis; TB, tuberculosis.

Figure 2. CD4 trends over time in overall, HIV-associated TB, DRESS and SJS/TEN phenotypes.



	BASELINE	6 MONTHS	12 MONTHS
OVERALL	115 (n=44, 62-175)	199 (n=16, 89-427)	319 (n=14, 134-439)
HIV/TB	90 (n=33, 61-142)	174 (n=12, 89-313)	351 (n=10, 137-439)
DRESS	121 (n=30, 68-167)	255 (n=12, 156-457)	388 (n=9, 314-605)
SJS/TEN	63 (n=11, 43-116)	97 (n=3, 58-267)	183 (n=4, 65-313)

Figure 2. CD4 trends over time in overall, HIV-associated TB, DRESS and SJS/TEN phenotypes. Median CD4 (cells/uL) counts at baseline, 6 months and 12 months for the overall cohort, co-infected subgroup and DRESS and SJS/TEN SCAR phenotypes with total number of samples and IQR. GFBDE CD4 trends were not included as there was limited CD4 information available for the three patients with this SCAR phenotype. DRESS, drug rash with eosinophilia and systemic symptoms; GBFDE, generalised bullous fixed drug eruption; HIV, human immunodeficiency virus; IQR, interquartile range; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TB, tuberculosis

SUPPLEMENTARY DATA

Table S1. Clinical characteristics and admission details by SCAR phenotype

Total	OVERALL 48	DRESS 32	SJS/TEN 13	GBFDE 3
Definite n (%)		14[1] (44%)	7 (54%)	
Probable n (%)		9[2] (28%)	3 (23%)	
Possible n (%)		9[3] (28%)	3 (23%)	
BSA 30-50% n (%)[4]		4 (13%)	1 (8%)	1 (33.3%)
BSA ≥50% n (%)		15 (47%)	7 (54%)	2 (66.7%)
Liver Involvement (ALT>80)	25 (52%)	20 (63%)	4 (31%)	1 (33%)
Median ALT n(IQR)	84 (45 – 330)	219 (68 – 413)	43 (29 – 96)	60 (39 – 192)
Median Eosinophils n, (IQR)	1.06 (0.6 – 2.65)	1.72 (1.01 – 4.38)	1.06 (0.83 – 1.7)	0.35 (0.33 – 0.36)
Time				
Hospital LOS (Median days, IQR)	26 (10.75 – 47)	29.5 (10.75 – 48.25)	18 (13 – 31)	20 (14 – 24.5)
IMADR onset to discharge (median days, IQR)	34.5 (20.75 – 57)	44.5 (24.75 – 67)	22 (20 – 48)	26 (18.5 – 28)
Readmission to Dermatology n (%)	10 (21%)	8 (25%)	2 (15%)	0 (0)

Table S1. Clinical characteristics and admission details by SCAR phenotype. BSA was calculated using the rules of nine method at the most extensive phase of the SCAR. Liver involvement was defined as twice the upper limit of normal of the reference range of our laboratory (range 10-40). The peak eosinophil count during the admission was used to calculate eosinophil count.

[1] Definite: RegiSCAR score >5

[2] Probable: RegiSCAR score = 4–5

[3] Possible: RegiSCAR score = 2–3

[4] 10 patients had missing information regarding BSA

ALT, alanine transaminase; GBFDE, generalized bullous fixed drug eruption; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; IMADR, immune mediated adverse reaction; LOS, length of stay; IQR, interquartile range; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson Syndrome/Toxic epidermal necrolysis

Table S2. Implicated Drugs, SDC outcomes and discharge regimens

Highest Naranjo scoring drugs	OVERALL 48	DRESS 32	SJS/TEN 13	GBFDE 3
FLTD n (%)	38[1] (79%)	28 (88%)	9 (69%)	1 (33%)
Cotrimoxazole n (%)	32 (67%)	18 (56%)	11 (85%)	3 (100%)
ART n (%)	16 (33%)	11 (34%)	4 (31%)	1 (33%)
Sequential Drug Challenge	35[2] (73%)	26 (81%)	8 (62%)	1 (33%)
FLTD drug SDC n (%)	30[3] (86%)	23 (88%)	6 (75%)	1 (100%)
Positive reaction to FLTD SDC n (%)	17/30 (57%)	15/23 (65%)	2/6 (33%)	0/1 (0%)
Single FLTD reaction n (%)	10/17 (59%)	9/15 (60%)	1/2 (50%)	0 (0%)
Rifampicin Reacted and stopped n (%)	4/10 (40%)	4/9 (44%)	0 (0%)	0 (0%)
Isoniazid reaction and stopped n (%)	2/10 (20%)	2 (22%)	0 (0%)	0 (0%)
Pyrazinamide reaction and stopped n (%)	4 (40%)	3 (33%)	1 (100%)	0 (0%)
Ethambutol reaction and stopped n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rifabutin reaction and stopped n (%)	1 (10%)	1 (11%)	0 (0%)	0 (0%)
Multiple FLTD drug reaction n (%)	7/17 (41%)	6/15 (40%)	1/2 (50%)	0 (0%)
Rifampicin/INH/ethambutol n (%)	1	1	0	0
Rifampicin/ethambutol n (%)	1	1	0	0
Rifampicin/INH (as fixed drug combination) n (%)	1	1	0	0
Rifabutin/INH/ethambutol n (%)	1	1	0	0
Rifabutin/ethambutol n (%)	1	1	0	0
Pyrazinamide/INH n (%)	1	0	1	0
Pyrazinamide/ethambutol n (%)	1	1	0	0
TB, no SDC	7/37 (19%)	5 (11.4%)	2 (11.8%)	0 (0%)
Death prior to SDC n (%)	2 (29%)	1 (20%)	1 (5.8%)	0 (0%)
TB diagnosis refuted n (%	1 (14%)	0 (0%)	1 (5.8%)	0 (0%)
Modified regimen due to organ damage n (%)	3 (43%)	3 (60%)	0 (0%)	0 (0%)
Unknown outcome n (%)	1 (14%)	1 (20%)	0 (0%)	0 (0%)
TB Discharge regimen[4]	34	25	7	2
RHZE n (%)	7 (21%)	2 (8%)	3 (43%)	2 (100%)
RHZE or Rifabutin/HZE n (%)	8 (24%)	3 (12%)	3 (43%)	2 (100%)
Continuation phase (RH alone) n (%)	5 (15%)	4 (16%)	1 (14%)	0 (0%)
Any FLTD including Rifabutin n (%)	22 (65%)	16 (64%)	4 (57%)	2 (100%)
Rifampicin included n (%)	15 (44%)	8 (32%)	5 (71%)	2 (100%)
Rifabutin included n (%)	4 (12%)	3 (12%)	1 (14%)	0 (0%)
Rifampicin OR Rifabutin included n (%)	19 (56%)	11 (44%)	6 (86%)	2 (100%)
Isoniazid included n (%)	19 (56%)	12 (48%)	5 (71%)	2 (100%)
Rifampicin/Rifabutin OR INH n (%)	22 (76.1%)	14 (73.5%)	6 (80%)	2 (100%)
Pyrazinamide Included n (%)	21 (65%)	15 (60%)	4 (57%)	2 (100%)
Ethambutol Included[5] n (%)	15 (44%)	8 (32%)	5 (71%)	2 (100%)
As part of first-line regimen n (%)	12 (80%)			
As part of modified regimen n (%)	3 (20%)			
No-FLTD in regimen n (%)	12 (33%)	11 (44%)	1 (14%)	0 (0%)

Table S2. Implicated drugs, SDC outcomes and discharge regimens. Supplementary table 2 shows the drugs implicated in the SCAR overall and per SCAR phenotype as well as the outcomes of SDC. TB discharge regimens shows the number of times each drug or combination of drugs was included in a discharge regimen.

[1]One patient without TB had a reaction to isoniazid while on isoniazid preventative therapy

[2]35 patients in total underwent SDC of any kind. A total of 13 patients never underwent SDC, seven of which are described in the TB, no SDC section. Of the remaining six: three had cotrimoxazole related SCAR with no rechallenge, one was related to nevirapine and INH prophylaxis, and two were unknown.

[3]Only 30 patients underwent SDC to FLTD, the remaining five were to non-FLTD drugs: three patients were rechallenged on TEE (one initially on nevirapine based ART, and two on TLD); one patient on TLD was rechallenged with TLD; and one patient who had a suspected SCAR to cotrimoxazole or vancomycin underwent a vancomycin SDC.

[4]Numbers used are those that were discharged on any TB regimen alive; of three patients who did not receive discharge regimen, one patient had their TB diagnosis refuted and two patients died during their admission

[5]Ethambutol is included in both first-line TB regimens and often included in modified or second-line regimens

ART, antiretroviral therapy; DRESS, drug rash with eosinophilia and systemic symptoms; E, ethambutol; FLTD, first-line anti-tuberculosis drugs; GBFDE, generalized bullous fixed drug eruption; H/INH, isoniazid; R, rifampicin; SCAR, severe cutaneous adverse reaction; SDC, sequential drug challenge; SJS/TEN, Stevens-Johnson Syndrome/Toxic epidermal necrolysis; TB, tuberculosis; TEE, tenofovir/emtricitabine/efavirenz fixed dose combination; TLD, tenofovir/lamivudine/dolutegravir fixed dose combination; Z, pyraziname

Table S3: Logistic regression model with death status as outcome.

Variable	Level	Univariable	Multivariable		
		OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**
Gender	Female	1			
	Male	0.77 (0.17 – 3.54)	0.734		
Age (years)		1.01 (0.94 – 1.08)	0.823	0.96 (0.87 – 1.051)	0.365
Validated phenotype	DRESS	1			
	TEN	2.7 (0.58 – 12.51)	0.204		
BSA		1.03 (0.99 – 1.06)	**0.143**	1.04 (1.00 – 1.08)	0.055
Highest ALT		0.99 (0.98 – 1.00)	**0.092**	0.99 (0.97 – 1.00)	**0.041**
Peak eosinophil		0.82 (0.47 – 1.42)	0.479		
HIV-associated TB	No	1			
	Yes	4.16 (0.47 -36.96)	0.201		
TB	No	1			
	Yes	3.26 (0.36 - 29.24)	0.291		
Pre-SCAR ART exposure	No	1			
	Yes	1.6 (0.29 -9.01)	0.591		
Baseline CD4 count		1.00 (0.99 – 1.00)	0.377		

Table S3: Logistic regression model with death status as outcome. Although not meeting statistical significance, the key finding of this multivariable analysis with death as outcome was the association of a slight increased risk of death with increasing disease severity (higher ALT and body surface area involvement).

ALT, alanine transaminase; ART, antiretroviral therapy; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; HIV, human immunodeficiency virus; OR, odds ratio; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TB, tuberculosis

Supplementary Methods

Data collection, definitions, and analysis

Baseline TB, HIV and SCAR admission data was collected retrospectively through the IMARI registry. Baseline was defined as the period six months preceding SCAR and up to three months post-onset of SCAR. Baseline variables included: demographics (age and gender) and medical history. Medical history included details of previous and current TB (including site-of-disease, method of diagnosis and starting treatment regimen). Site-of-disease was determined based on clinical records and laboratory results where appropriate and was separated into two categories, pulmonary tuberculosis and extrapulmonary tuberculosis. Extrapulmonary tuberculosis was defined as any TB found outside of the lungs including, but not exclusive to pleural disease. This was based on laboratory evidence of disease outside the lungs (ie nucleic acid amplification tests), imaging or on robust clinical opinion.

HIV details pre-admission included date of diagnosis, CD4 count, viral load (VL) and ART. Date of diagnosis was based on records on the National Health Laboratory Services (NHLS) or clinical folder review where this was available on the NHLS platform. CD4 and VL were recorded as baseline if they had been taken in the six months prior to onset of SCAR or in the three months post-onset of SCAR if they had not been performed prior.

SCAR admission variables included onset of reaction, clinical and laboratory markers of phenotype and severity (including BSA involvement, ALT, and peak eosinophil count), hospital length of stay (LOS), and SDC outcomes. Onset of reaction was determined based on patient report or on first clinical review when this was not certain. BSA was determined and recorded on all patients using the Wallace Rule of Nines[34]. The peak ALT and eosinophil count at any point during admission were captured. Hospital LOS was defined as date of admission to date of discharge. Table 1 documents these outcome measures and definitions further.

Long-term TB and HIV outcomes were collected retrospectively at 6- and 12-month time-points after the date of discharge from SCAR hospitalisation. Virological suppression was defined as <400 copies/ml. This value was used due to various different laboratory assays used over the period of collection.

To minimise missing data, several methods were used to collect outcome data including folder and drug allergy clinic record review, visit-tracking on the Clinicom hospital booking system, and the provincial Single Patient Viewer (SPV). Clinicom and SPV are electronic medical record systems tracking all patient encounters across various levels of the healthcare service in the Western Cape province. Additionally, SPV captures drug dispensing and laboratory information. The National Health Laboratory Services (NHLS) electronic results platform was searched for all HIV/TB laboratory testing performed at all levels of care during the 12-month follow-up period. Patients were either followed up at the admitting facility at the drug allergy clinic, another specialist clinic (ie Infectious Diseases) or their local primary care facility. Due to this variability, which included the caring clinician at these visits, follow-up bloods were often taken early or delayed. For this reason, the six-month bloods were defined as bloods taken in the period six ± three months (ie three months to nine months post-SCAR) and the 12 month bloods defined as 12 ± 3 months (ie nine months to 15 months post-SCAR). Figure 1A further describes TB and HIV outcome definitions used, and the window period allowed around 6- and 12-month time-points for key outcome variables. Loss-to-follow-up (LTFU) was defined as no medical encounter or pick-up of medication for three consecutive months. All data was stored on a password protected electronic database (REDCap 12.0.19 - © 2022 Vanderbilt University), and de-identified data was exported for analysis on Microsoft Excel, version 16.54 (Microsoft Corporation ©, 2021) and STATA, version 15.1 (StataCorp.

2017. College Station, TX: StataCorp LLC.). All predictor variables with a p-value < 0.2 in univariable logistic regression models were used to build multivariable logistic regression models using a forward stepwise method at 0.05 level of significance. A variable that did not improve the model fit was dropped.

APPENDICES AND SUPPORTING MATERIAL

RESEARCH PROTOCOL

LONG-TERM HIV AND TUBERCULOSIS OUTCOMES IN CO-INFECTED PATIENTS WITH TREATMENT-LIMITING SEVERE CUTANEOUS ADVERSE REACTIONS

A sub-study of:
Prospective longitudinal study of sequelae associated with severe cutaneous adverse drug reactions (HREC 270/2020)

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ABBREVIATIONS

ADR	adverse drug reaction
ARV	antiretroviral
DRESS	Drug reaction with eosinophilia and systemic symptoms
EWI	early warning indicator
FLTD	first line tuberculosis drugs
HIV	human immunodeficiency virus
HREC	Health Research Ethics Committee
HADS	hospital anxiety and depression scale
IM-ADR	Immune-mediated adverse drug reaction
IMARI-SA	Immune-mediated Adverse drug Reactions in African TB/HIV endemic settings
LTFU	loss to follow up
NHLS	National Health Laboratory Services
PLWHIV	people living with HIV
QoL	quality of life
SCAR	severe cutaneous adverse reaction
SJS	Steven-Johnson syndrome
SPV	Single Patient Viewer
TB	tuberculosis
TEN	Toxic epidermal necrolysis
VL	viral load
WHO	World Health Organisation

BACKGROUND

South Africa has one of the highest burdens of tuberculosis (TB) globally with an estimated 360 000 cases in 2019, of which 58% were coinfected with the human immunodeficiency virus (HIV)[1]. The Western Cape, and the Cape Town metropolitan area in particular, is especially affected[2]. Management of these patients is an enormous public health concern, and can be challenging with multiple drug-drug interactions, polypharmacy and a large spectrum of adverse drug reactions (ADR) that often necessitates treatment interruption or a change in regimen to less efficacious and potentially more toxic drugs[3,4]. Furthermore, it is well known that HIV co-infected patients are more prone to adverse drug reactions (ADR) with some studies estimating a 10 -100-fold increase in incidence in these patients[5,6]. Severe cutaneous adverse reactions (SCAR) account for a significant amount of these ADRs and although often mild, can increase morbidity and in severe cases may even be fatal[7]. The major phenotypes include Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). The divisions of dermatology and immunology at Groote Schuur Hospital, a tertiary hospital in Cape Town, have over the years gained much experience in the management of these immune-mediated (IM) ADRs and have successfully and safely rechallenged many patients, often with the culprit drug being successfully reintroduced in many circumstances. They have established the Immune-mediated Adverse drug Reactions in African TB HIV endemic settings (IMARI-SA) registry and biorepository and have already obtained Health Research Ethics Committee (HREC) approval (HREC 270/2020) to study the long term outcomes in patients with SCAR.

In 2013, a local epidemiological review showed an approximately 80% cure or treatment completion rate in HIV and TB coinfected patients in the Western Cape[8] with a similar national rate in 2018 documented by the WHO in their Tuberculosis Global Report in 2020[1]. However, the long-term outcomes and success rates post-SCAR to FLTD are not well known. It is postulated that these outcomes are poorer given the need for prolonged treatment interruption; prolonged hospitalization for both stabilization after initial SCAR and then for observation during rechallenge; and potentially changing to less efficacious regimens with a higher pill burden and often prolonged courses. In a retrospective study of cutaneous adverse drug reactions to FLTD in the dermatology unit at Groote Schuur, Knight et al demonstrated a high proportion of patients discharged on TB treatment after having undergone successful rechallenge of these drugs (88%); however, only 51% were discharged on FLTD and the remaining required a second line agent[9]. Despite this relative success, there are no studies demonstrating outcomes after reinitiating anti-tuberculosis therapy or immunological/virological status at time points further from the index SCAR admission. Similarly, South Africa's antiretroviral (ARV) rollout program, one of the largest in the world, has been largely successful with approximately 62% of people living with HIV (PLWHIV) on ARVs, of which sustained virological suppression was achieved in approximately 90% when a viral load (VL) of less than 1000 copies RNA/ml is used as a determinant of virological supporession[10,11]. This was confirmed in a local analysis of patients entering into adherence clubs in Khayelitsha, a high density township in Cape Town[12]. In contrast, several studies have demonstrated that loss to follow up (LTFU) is increased when ARV therapy is initiated in-hospital rather than a primary health care setting [13,14]. Adverse drug reactions are another common cause of poor adherence to treatment. However, adherence to ARV therapy and sustained virological suppression after prolonged hospitalization secondary to SCAR are unknown.

The short term and long-term sequelae of SCAR are well documented and involve multiple systems. The breakdown of the skin barrier can result in sepsis which is a major risk factor for mortality in the acute setting. Acute renal impairment, gastrointestinal complications, pulmonary and ophthalmic lesions also occur causing significant morbidity. However, late complications can occur even after successful treatment and re-epithelialisation has occurred. Even after a disease-free period of months to years, severe sequalae may ensue. In SJS/TEN, the ocular sequelae are significant and can result in permanent visual loss, genitourinary complications include male genital synechiae and vaginal canal stenosis, endometriosis and vulvovaginal adenosis. Interstitial lung disease, bronchiectasis, bronchiolitis obliterans and airway stenosis have been documented after resolution of SJS/TEN[15,16]. DRESS is also associated with complications after resolution of the original insult. Autoimmune diseases are the major sequalae in this group and range from asymptomatic with the emergence of autoantibodies to disease. Autoimmune thyroid disease is the most common manifestation, but type 1 diabetes mellitus has also been reported. Although rare, other autoimmune diseases have also been reported such as sclerodermoid graft-versus-host disease like lesions, lupus erythematosus, autoimmune haemolytic anaemia and rheumatoid arthritis [17].

Neurospychiatric sequelae following an admission for SJS/TEN have also been identified. Although most research appears to be qualitative in nature [18,19], the use of validated scoring systems, such as the Kessler K-10 psychological distress questionnaire and hospital anxiety and depression scale (HADS), have been used across multicultural settings to provide quantitative data [20,21]. Quality of life (QoL) is also affected in patients particularly in the SJS/TEN group [22]. These complications are often neglected. However, understanding the psychosocial effects of these conditions would provide a platform to offer a more holistic therapeutic approach.

Despite being well documented, the long-term complications are often overlooked because of the disease-free period between the initial SCAR and onset of complications. Furthermore, much of what is known about these illnesses are from studies done in Europe and Asia, and there is very little data with regards to the African context, especially within the HIV/TB setting. This review aims to address some of those gaps and provide a bridge for further research.

AIMS AND OBJECTIVES

To evaluate the long-term HIV and TB infection outcomes amongst a cohort of patients (from the IMARI study registry) admitted to hospital with SCAR

1. Describe TB treatment regimens and 6 and 12-month TB cure (sputum culture conversion) and completion rates in patients admitted to hospital with SCAR
2. Describe HIV and ART treatment outcomes at 6 and 12-month post SCAR admissions, including ART regimens, viral load and CD4 counts.

METHOD

1. Patients

1.1. Inclusion criteria

1. Patients consented to be part of the IMARI registry and biorepository (HREC: R031/2018)
2. Treatment-limiting SCAR requiring hospitalization
3. Age ≥12 years

1.2. Exclusion criteria

1. Patients not involved in the IMARI registry and biorepository
4. Age < 12 years

No informed consent

2. Outcome Measurement

This sub-study of the IMARI registry will review the longitudinal data collected at baseline and specific time points after the onset of SCAR. Table 1 illustrates these time points and specific outcomes measured.

	Long term outcome(s)	Measures	Timeframe from IM-ADR
TB	• TB treatment non-compliance • Sputum culture conversion • TB recurrence rates • Altered anti-TB multiple drug regimens • Prolonged treatment interruption • Drug resistance	WHO treatment outcome definitions of treatment completed, interrupted (>2 months), or cured; sputum conversion, recurrence rate. Drug resistance rates (via either culture or NAAT)	0, 6 and 12 months. Sputum conversion at 2 and 5 months. Recurrent disease within 2 years.
HIV	• Viral control • CD4 cell count recovery/immune reconstitution • ART drug resistance	Viral load (aligned to SA National programme) CD4 count Switch to 2nd or 3rd line ART	0 and 12 months 0, 12 and 24 months Switch to 2nd line ART within 2 years

The TB measurement outcomes will be based on the World Health Organisation (WHO) definitions of cure, treatment completion or failed, treatment success or LTFU for drug sensitive TB and where applicable, the respective definitions for mono-resistant TB and multi-drug resistant TB (MDR-TB) (See appendix for full definitions of treatment outcomes in drug sensitive (appendix Table 1) and drug resistant TB (appendix Table 2)). Where sputum culture results are not available at end of treatment, treatment completion could be used as a surrogate marker if there is documented completion of appropriate duration of therapy with clinical and/or radiological improvement.

Outcomes related to HIV will be based on the WHO definitions of virological failure (>1000 copies RNA/ml on two consecutive occasions three months apart), immunological failure (CD4 count falls below baseline or persistently lower than 100 cells/mm^3). Drug resistance patterns and mutations are not routinely performed, but the WHO has validated early warning indicators (EWI) that are associated with increased risk of HIV drug resistance, which include virological suppression, retention in care, pharmacy stock-out, pharmacy dispensing practices and on-time pill pick-up[23]. These indicators, where available on electronic platforms, and a change in regimen to 2nd or 3rd line agents will be used as surrogate markers for drug resistance.

3. Data collection

Routine clinical and laboratory data from both clinical and electronic records will be collected from patients entered into the IMARI registry and biorepository and who meet inclusion criteria for this retrospective observational study. Information regarding patient demographics, medical and drug history, admission history and subsequent medical course will be obtained, specifically looking at information pertaining to subsequent IM-ADRs or sequelae from initial ADR, HIV virological and immunological status and current and prior antiretroviral regimens, TB outcomes including regimen changes and cure/treatment completion rates. Laboratory data will be obtained via the National Health Laboratory Service (NHLS). Other secure electronic pharmaceutical and electronic records may also be used like Single Patient Viewer (SPV) and Clinicom. These platforms track patient encounters with the health care system. The provincial death register will also be accessed to obtain mortality statistics where there has been loss to follow-up.

4. Timeline to completion

	HREC Submission	Data Collection	Data analysis	Write-up	Submission
Timeline	August 2021	Sep-Dec 2021	Jan-Apr 2022	May-June 2022	July 2022

5. Impact of research

This research is novel in that there is limited data on the long-term outcomes of individuals with HIV/TB co-infection following a SCAR. To our knowledge there is no existing literature on this topic from a HIV/TB endemic area and it would provide valuable insight into these outcomes, particularly in our setting. Gaining a deeper understanding of these long-term complications would also allow the development of guidelines that would improve patient care and hopefully mitigate some of these complications.

ETHICS

1. Consent

All patients entered into the IMARI registry and biorepository (HREC: R031/2018) have given written informed consent for the long-term collection of clinical data (HREC 270/2020)

2. Patient confidentiality and data security

This study is a sub-study of the IMARI registry and biorepository. Data included in this study is captured in a de-identified manner. All information is entered into a secure, password protected electronic database (RedCap) accessible only to investigators on the IMARI study. Subsequent clinical and laboratory data may be obtained from electronic platforms where patient details are present, however, no patient-identifying data will be captured. All electronic platforms used for this purpose are password protected and require prior authorization to access this information.

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APPENDIX

Table 1. WHO treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.

Table 2. WHO Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion by the end of the intensive phase, or – bacteriological reversion in the continuation phase after conversion to negative, or – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or – adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed.

ETHICS APPROVAL

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 September 2021

HREC REF: 577/2021

A/Prof J Peter
Division of Allergy & Clinical Immunology
H-Floor, OMB
Email: jonny.peter@uct.ac.za
Student: Simon.veenstra@westerncape.gov.za

Dear A/Prof Peter

PROJECT TITLE: LONG-TERM HIV AND TUBERCULOSIS OUTCOMES IN CO-INFECTED PATIENTS WITH TREATMENT LIMITING SEVERE CUTANEOUS ADVERSE REACTIONS-MMED CANDIDATE-DR SIMON VEENSTRA-SUB-STUDY LINKED TO R031/2018

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020: 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 September 2022.

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

The HREC acknowledge that the student: - Dr Simon Veenstra will also be involved in this study.

Please quote the HREC REF 577/2021 in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC/REF 577/2021sa

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 577/2021sa

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30-9-23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	14/9/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to 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

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	13 September 2022		
HREC REF Number	577/2021	Current Ethics Approval was granted until	30 Sep 2022
Protocol title	Long-term HIV and tuberculosis outcomes in co-infected patients with treatment-limiting severe cutaneous adverse reactions – Mmed Candidate – Dr Simon Veenstra – Sub-study linked to R031/2018		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	☐ Yes	✓ No	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note**: A separate FHS016 must be submitted for each sub-study.	N/A		
Principal Investigator	Associate Professor Jonathan Peter		
Department / Office Internal Mail Address	Department of Allergy & Clinical Immunology, Groote Schuur Hospital, Observatory, 7925.		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No

1.2 If the 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-submission@uct.ac.za)	☐ Yes	☐ 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:

Submission Type	*Description*	*New fee (Vat Incl.)*	*tick ✓*
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**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 Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

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	N/A
Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	
Email Address	

2. Internal Journal Billing:	
Fund Number:	N/A
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

N/A

3. Protocol status (tick ✓)

☐	Open 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
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	64
Number of participants enrolled, since last HREC Progress report (continuing review)	64
Additional number of participants still required	0

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	85
Number of participants determined to be ineligible (i.e. after screening)	21
Number of participants currently active on the study	64

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

Number of participants completed study (without events leading to withdrawal)	64
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.	30
No longer in clinical care	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	12
Death	

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:
This research is currently in the data analysis and write-up phase. The main findings suggest that treatment-limiting SCARs contributes to HIV-related mortality, and where FLTDs are implicated, worsen the complexity of anti-TB drug regimens and treatment completion. There is a high mortality rate and poor retention in care at 1 year amongst this cohort.

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 acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet 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).

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

Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked 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.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ 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

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	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

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

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.
N/A

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**		
☐ Yes	✓ No – The IMARI Parent study has active UCT no-fault insurance, therefore, no insurance is required for this sub-study	☐ Not Applicable – N/A

If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	

For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@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 Application Form FHS013):	
N/A	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	13 September 2022

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

INSTRUCTIONS FOR AUTHORS: THE INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE

The International Journal of Tuberculosis and Lung Disease

INSTRUCTIONS FOR AUTHORS

The International Journal of Tuberculosis and Lung Disease (IJTLD), publishes Editorials, Original Articles, Minireviews, Letters and Correspondence of significance on TB and the entire spectrum of lung diseases in adults and children. The IJTLD welcomes submissions on basic, translational, clinical, epidemiological and programmatic research relevant to the Union's mission to find health solutions for these conditions, including the development of vaccines, diagnostics and medicines for the prevention, management and control of TB and other respiratory diseases.

SUBMISSION OF ARTICLES

Articles should be submitted online via Manuscript Central: http://mc.manuscriptcentral.com/ijtld.

Before submitting your article, please read and carefully follow the Instructions for Authors outlined below.

All articles must be submitted in English. When necessary, authors are encouraged to seek professional editing service before submission. If the quality of the English is not considered to be adequate, the manuscript will be returned the authors without review. Authors may be offered the opportunity to re-submit a revised version that has been edited for English language.

Manuscripts may only be actively under consideration by one journal at any given time.

FAST TRACK REVIEW

For exceptional articles of major scientific or public health interest, the Editor-in-Chief may decide to proceed with fast-track review, aiming to reach a first decision within one week. If you believe your article requires fast-track review, please state this in the cover letter of your manuscript along with detailed justification(s).

AUTHORSHIP

The journal recommends the International Committee of Medical Journal Editors' criteria for authorship (http://www.icmje.org/recommendations/browse/roles-andresponsibilities/defining-the-role-of-authors-and-contributors.html). The ICMJE recommends that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

When a multicentre group has conducted the study, all individuals who accept direct responsibility for the manuscript should be identified. When submitting a group author manuscript, the corresponding author should clearly identify all individual authors, as well as the group name.

FORMAT OF SUBMITTED ARTICLES

The formats for different types of articles are summarised as follows:

Article type Word limit Figure or Table* References Online Supplementary Data Abstract Original Article (including also Systematic Reviews and Meta-Analysis) 2500 5 35 (70 for Systematic Reviews and metaanalyses) Accepted Yes (200 words) Review (State of the Art, Guidelines/Consensus) 3500 5 70 Accepted Yes (200 words) Minireview 2000 3–4 40 Accepted Yes (200 words) Letter 1100 1 15 Accepted No Correspondence 600 1 10 Not accepted No Editorial 500- 1400 1-2 25 Accepted No * Number stated refers to the maximum number of figures and/or tables combined.

Original Articles and Reviews

Original Articles (including also Systematic Reviews and Meta-Analyses) should not exceed 2,500 words (excluding abstract, references, Tables and Figure captions) and should have a structured summary of 200 words, up to 35 references and between 5 moderate-sized tables/figures. Please see examples of table sizes that will fit this layout within the section 'Figures and Tables'. Tables that are too large to be published on a print journal page should be included as Supplementary Data (see details below).

Clinical trials must be registered in a WHO compliant clinical trial registry and reported according to CONSORT guidelines. Epidemiological studies should be conducted and reported according to STROBE guidelines. Systematic reviews and Meta-Analyses will only be considered if they provide insight beyond that available in the source studies. Reporting should follow PRISMA guidelines. Meta-Analysis of observational data should follow MOOSE guidelines. A completed PRISMA or MOOSE checklist should be included with the submission.

Abstract

An informative abstract of no more than 200 words that can be understood without reference to the text should be included. For optimal clarity, the author should use the headings Background, Methods, Results and Conclusion. Abstracts will be translated into French (authors are welcome to provide their own translation).

Main text headings: Three categories of heading are used.

Major headings (e.g., METHODS, RESULTS) are in Arial 12 bold caps.

Minor heading 1 (e.g., Study population and materials) in Arial 12 italics.

Minor heading 2 (e.g., Human subjects) in Times Roman 12 italics.

Sections should follow the usual conventions

Introduction (does not require a heading): This should include the aim, objectives and/or hypotheses for the manuscript, preceded by their rationale.

Methods: This should include a description of the study design, study population, intervention, exposures, outcomes and other relevant variables, where applicable. Details of the statistical analysis plan and sample size and study power should also be included. Methods should be described in a manner that is conducive to replication.

Details of ethics approval (or a statement as to why it was not required) should be provided in the Methods section of all research studies. All studies involving human subjects should include details of informed consent.
Results: Present the results in logical sequence, referencing figures and tables (see information below on submitting figures and tables). For complex tables only highlight the most important results.

Discussion: Bring the reader back to your initial aims, objective or hypothesis, showing how this study has improved our understanding of the topic.

Conclusions: optional, but if used, please briefly highlight the single most significant aspect of this study.

Reviews (State of the Art, Viewpoints, Guidelines) are aimed to inform and educate readers and should stimulate debate around clinical and scientific topics. The IJTLD also welcomes suggestions for review articles on different aspects of TB and across the breadth of respiratory medicine. Authors proposing an unsolicited review should explain in a cover letter why the topic is timely and relevant and include a maximum of 5 examples of their own recent published work supporting their expertise in this field.

Submitted reviews should not overlap with recently published ones on similar topics. Review articles should represent the state of the art in their specific field. The literature review should be up-to-date. Systematic review methods are encouraged but are not mandatory. The IJTLD strongly encourages the use of new imaginative figures and of a pivotal figure to summarise key concepts or conclusions of the review.

Review articles (see Table above) should not exceed 3,500 words (excluding abstract, references, tables and figure captions) and should have a structured summary of 200 words, up to 70 references and 5 moderate-sized tables/figures.

Minireviews are focused, expert reviews on cutting-edge issues. One-page proposals will be considered, and will be judged on 1) the scientific importance and novelty of the subject matter, 2) its relevance to the readership of the Journal, and 3) the expertise of the proposed authors. Minireviews are expected to draw conclusions and make recommendations that are based on the evidence presented.

Text up to 2,000 words, a structured summary of 200 words, 3–4 moderate-sized tables/figures and up to 40 references.

Forum: Letters and Correspondence
Letters include research letters, case studies and other forms of short communication to the Editor. Research letters are preliminary studies or short reports presented in the shorter format of a Letter to the Editor. Case studies are considered only if they contain original and innovative material, ideally discussing cases in the form of a mini-review of the available literature on the topic. Patient consent should be provided (or, in the case of death, the consent of a relative). Letters do not include an abstract or text headings and start 'Dear Editor,…'. They should not exceed 1,100 words (excluding references, tables and figure captions) and should have no more than 15 references. One figure or one table is mandatory.

Correspondence is designed to discuss relevant articles, guidelines, documents or other topical matters recently published in the IJTLD, or other journals or media. Correspondence in response to an article published

in the IJTLD should be submitted within 3 months of the publication date of the original article. All Correspondence is sent to the authors of the original article for a reply and these exchanges are prioritised for publication in the next available issue of the Journal. Correspondence does not include an abstract or text headings and starts 'Dear Editor, …'. They should not exceed 600 words (excluding references, tables and figure captions) and should have no more than 10 references. One figure or one table is highly recommended.

Editorials

Editorials are usually invited by the Editorial Board to allow experts to concisely discuss the findings of an Original Article (sharing their perspective on how the publication advances the field and highlighting the need for specific further research). Unsolicited Editorials are also of interest and can highlight a key initiative or paradigm shift. Editorials do not include an abstract and are between 500–1,400 words (excluding references, tables and figure captions) and should have no more than 25 references and 1-2 figures/tables.

Papers that do not conform to these guidelines will either be rejected, or returned to the authors for revision prior to peer review.

FORMATTING

Authors should submit a single Word document (.doc or .docx) – this document should include the title page, abstract text, references, tables and figures with legends. For ease of peer review, the article should have 1.5 or double spacing and continuous line numbering.

Title page: This should contain:

1) a concise, informative title of not more than 110 characters and spaces, without abbreviations
2) the names and affiliations of all contributing authors, clearly indicating who is linked to each institution
3) a running head of not more than 45 characters and spaces
4) a word count of the summary, a word count of the text, number of references, tables and figures
5) 3-5 keywords that do not appear in the title
6) the name, full address and contact details of the corresponding author.

ACKNOWLEDGEMENTS: Acknowledge only those people who have made substantial contributions to the study, with their consent. All sources of support in the form of grants, author contributions and all conflicts of interest should also be mentioned.

REFERENCES: The accuracy of references is the responsibility of the author. Please use superscript numbers in the text, and they must be numbered in the order in which they are cited. References that are cited more than once retain the same number for each citation. The references list at the end of an article should be arranged in numerical order.

References to an article: should include the names of the authors, followed by their initials. List all authors when three or fewer - see the example below:

Gordon JB, Bennett AM. Tuberculosis in reindeer. Scand Rev Respir Dis1978; 96 (Suppl): 217-219.

When there are more than three authors, list only the first author and add 'et al.'

References to a piece of work: (book/monograph) should include the names of the authors, the title of the piece of work, the ISSN number of the publication, the name of the Editor, the place and year of publication, the number of the volume and the first and last page numbers.

References to a chapter in a book: should include the names of the authors, the title of the chapter with the word "In" preceding the reference of the work e.g. Girling DJ. The chemotherapy of tuberculosis. In: Ratledge C, Stanford J, Grange JM, eds. Biology of the mycobacteria. London, UK: Academic Press, 1989: pp 285-323.

Electronic references should be given only when an original citation is unavailable; please provide as much information as possible, including html address. References to an article yet to be published: should give the name of the journal as '(In Press)' and include the article DOI.

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FIGURES AND TABLES

Tables and figures should be self-explanatory and easily understood as a standalone element. Numbering of tables/figures corresponds to where they are first cited in the text. All abbreviations included in the title or in the Table/Figure, even if explained in the text of the article, should be expanded in a footnote to be understandable without referring to the text.

Tables: A short descriptive title should appear above the table. Each column should have a short or abbreviated heading. All abbreviations should be explained in a clear legend below the table. Tables should not have shading or bolding.

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Examples of table sizes:
Small table with 4-5 columns and 4-5 rows = 1/4 page in a typeset article
Moderate table with 4-6 columns and 10-12 rows = 1/2 page in a typeset article
Large table with 6-10 columns and 12-16 rows = 1 full page in a typeset article

If there is the need to refer to very large datasets, the excess material can be included as Supplementary Data (please note charges below). The figures and tables in Supplementary Data should be numbered as Figure S1, Table S1 etc (to avoid confusion over labelling of the figures and tables in the main body of the article). Alternatively, the data can be hosted via a service such as Figshare (https://figshare.com) with a link embedded in the text.

Figures: These should be referred to consecutively in the text. They can be inserted into the Word document at the end of the References or uploaded separately as image files (.jpg, .ppt, .gif, .tif or .bmp). A brief explanatory legend should be provided for every figure to ensure it can be understood as a standalone item.

After acceptance, figures should be made available in editable form for typesetting:
Line drawings, flow charts and histograms: Must be supplied either as .doc or .xls files. For optimal clarity they should be in black and white, with solid black lines, and avoid shading.

Scans, photographs, or X-rays: Should be supplied at a resolution of a least 300 dpi (preferably 500 dpi) as TIFF or JPEG files suitable for reproduction. Photo-micrographs should have internal scale markers where appropriate. X-ray fim should bring out the detail with the area of importance clearly indicated. Techniques (staining, magnification, etc) should be defined.

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Lettering: The size of the symbols and lettering should be in scale with the figure using black Arial font, of uniform size.

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Avoid abbreviations in the title or summary. Abbreviations or unusual terms should be described the first time of use. Symbols and units of measure must conform to recognised scientific use, i.e. SI units. For more detailed recommendations, authors may consult the Royal Society of Medicine publication Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors. Designation of diseases must conform to the International Classification of Diseases. Designation of micro-organisms must conform to the norms of biology. Proprietary names of drugs, instruments, etc. should be indicated by the use of initial capital letters. Names of instruments should be accompanied by the manufacturer's name, city, state and country.

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Manuscripts should conform to the Uniform Requirements for Manuscripts submitted to Biomedical Journals (http://www.icmje.org/index.html). Authors should ensure they follow the relevant recommendations and guidelines for reporting their findings (CONSORT, STARD, MOOSE, STROBE, PRISMA, STREGA). Articles on clinical research should conform to the standards defined in the Helsinki Declaration, as revised in 2013 (www.wma.net/en/30publications/10policies/b3/index.html).

Stigmatising language: Authors are advised to avoid terms that may be perceived to be stigmatising, such as "TB suspect" or "defaulter". Authors can refer to the following publications: Zachariah R. et al., Language in tuberculosis services: can we change to patient-centred terminology and stop the paradigm of blaming the patients? Int J Tuberc Lung Dis 2012; 16: 714–717

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All articles should be accompanied by the Author Checklist. The checklist will help authors to submit articles which follow the editorial rules of the IJTLD, thus minimising rejection based on non-conformity. Any specific issue related to the checklist should be addressed to the Editors-in-Chief in the accompanying covering letter. All other correspondence should be sent directly to: The Editorial Office, The Union, 2 rue Jean Lantier, 75001 Paris, FRANCE. e-mail: journal@theunion.org