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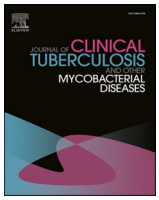

Long-term HIV and tuberculosis outcomes in patients hospitalised with severe cutaneous adverse reactions

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ABSTRACT

Background: Treatment-limiting severe cutaneous adverse reactions (SCAR) occur more commonly amongst persons with HIV-associated tuberculosis (TB). The impact of SCAR on long-term HIV/TB outcomes is unknown.
Methods: Patients with 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. 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 (eight co-infected with TB), were deceased at 12-months, and 12(25%) were lost to follow-up. Amongst TB-SCAR patients, seven (21%) were discharged on all four first-line anti-TB drugs (FLTD), while 12(33%) had 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 at 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.

1. Introduction

South Africa (SA) has one of the highest burdens of tuberculosis (TB) globally and coinfection with human immunodeficiency virus (HIV) exceeds 50% [[1], p. 18]. Management of HIV-associated TB poses 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), occur more commonly amongst persons with HIV-associated TB than those with TB alone, with IM-ADR occurring

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2–100-fold more commonly in persons living with HIV (PLWH) [3,4]. Treatment-limiting, life-threatening SCAR secondary to first-line anti-TB drugs (FLTD), cotrimoxazole and antiretrovirals cause many hospitalisations, resulting in considerable morbidity, prolonged hospitalisation, and healthcare expenditure [5]. 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].

TB treatment completion and cure rates approach 80% in HIV-associated TB patients in SA [[7,8], p. 104]. However, data is limited 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 [9] yet, despite 88% of TB-SCAR patients undergoing SDC, only half remain on at least one FLTD [5] and their treatment completion rates are unknown. SA has the largest antiretroviral therapy (ART) program in the world, with >60% of PLWH on ART and around 90% having sustained virological suppression [10,11]. With 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 [12,13]. This study aimed to describe the 6- and 12-month HIV and TB outcomes amongst patients hospitalised for HIV/TB-associated SCAR.

2. Methods

2.1. Patient selection and ethical approval

Patients with SCAR admitted to the dermatology ward of Groote Schuur Hospital (GSH), a tertiary hospital, in Cape Town, South Africa were reviewed for inclusion. In 2021, Cape Town city had an estimated population of 4.78 million people of which GSH serves approximately half [14]. At a provincial level, the estimated TB burden is one of the highest in the country [15]. SCAR patients were eligible for inclusion if they met the following criteria: i) > 12 years old, ii) either HIV-positive, active TB, 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) consented to collection of their clinical data. The study and 12-month follow-up period spanned three years from 1st October 2018 to 30th September 2021. Patients were prospectively enrolled and had baseline data, phenotype validation and drug causality assessment performed as part of the Immune-mediated adverse drug reactions (IMARI) Africa study (University of Cape Town (UCT) Human Research Ethics Committee (HREC): R031/2018). IMARI uses RegiSCAR [16,17] phenotype validation for SJS/TEN and DRESS, and Naranjo and/or Alden scoring tools for drug causality assessment [18,19]. GBFDE was diagnosed by a dermatologist. The UCT HREC approved this study (577/2021).

2.2. Data collection, definitions, and analysis

Baseline TB, HIV and SCAR admission data was collected 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). Long-term TB and HIV outcomes were collected at 6- and 12-month time-points after discharge from SCAR hospitalisation. Virological suppression was defined as <400 copies/ml. To minimise missing data, several methods were used to collect 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 record systems tracking patient encounters across various levels of healthcare services in the Western Cape province. Additionally, SPV captures drug dispensing and laboratory information. The National Health Laboratory Services electronic results platform was searched for all HIV/TB laboratory testing performed at all care levels during the 12-month follow-up period. Fig. 1A describes TB and HIV outcome definitions used, and the window period allowed around 6- and 12-month time-points for key outcome variables. 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. Variables that did not improve the model fit were dropped.

3. Results

3.1. Baseline characteristics and clinical information

Table 1 provides the baseline characteristics, and TB and HIV disease details for the cohort of 48 validated HIV or TB-associated SCAR patients, and Fig. 1B illustrates the stratification by phenotype (32 DRESS, 13 SJS/TEN and 3 GBFDE) and HIV/TB status (34 HIV-associated TB, 3TB-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, one was HIV-negative). 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 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) were 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; $P = 0.162$)].

Overall, 45 (94%) participants were HIV-positive. Forty-four had baseline median (IQR) CD4 cell counts around time of SCAR of 115 (62–175) cells/uL. Baseline VL results were only available for 15/45 (33%) within six-months pre- and three-months post-SCAR, but it is notable that only one of seven VLs available pre-SCAR had virological suppression. Nine patients had VL performed (one 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 [20]. Cotrimoxazole prophylaxis had been prescribed for 29/34 (85%) of patients with CD4 cell count <200cells/uL.

3.2. SCAR phenotypes and offending drugs

Supplementary Table 1 details 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 phenotypes. 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) LOS was 26

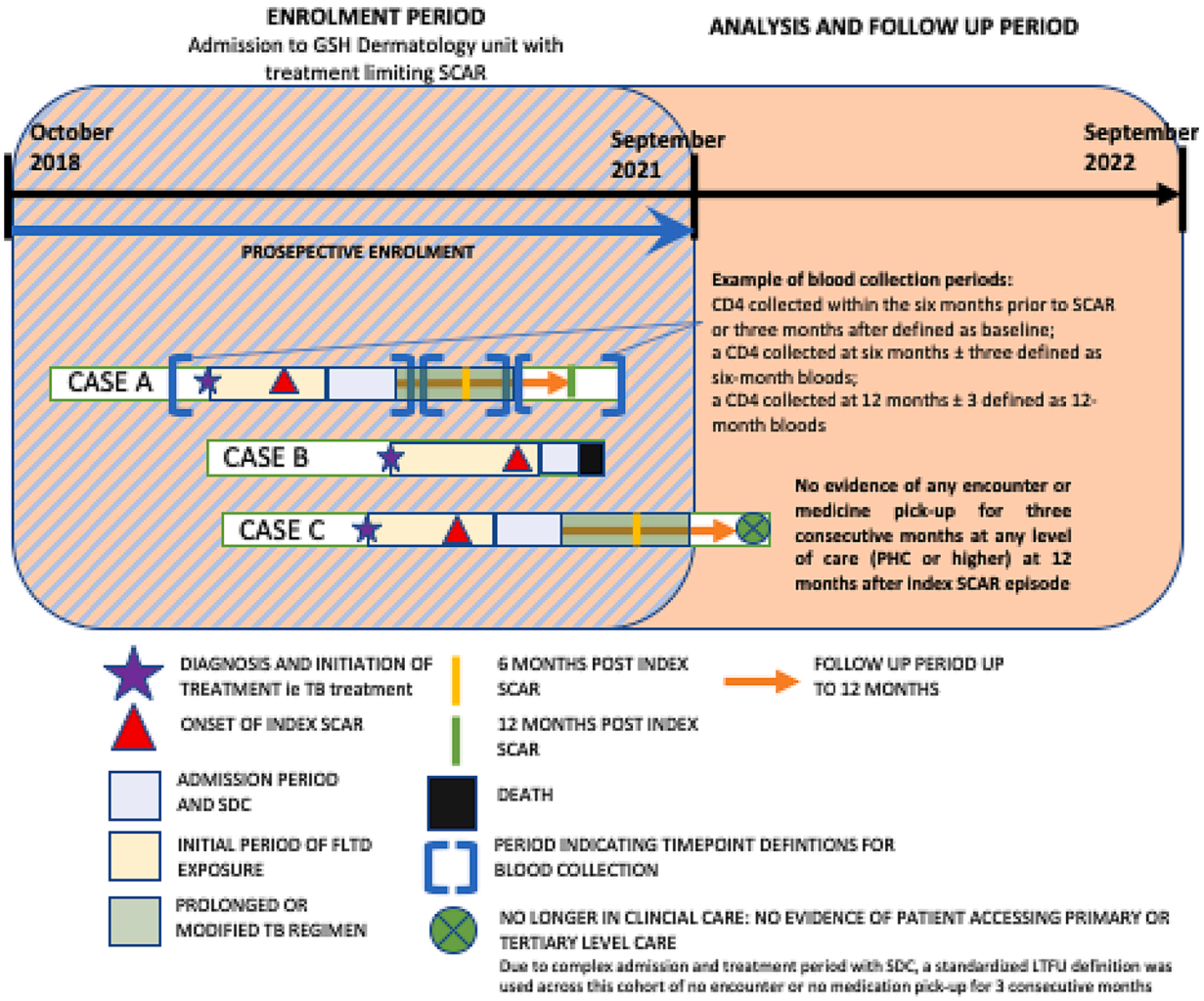

Fig. 1A. Explanations of study period, sampling windows and outcomes. The study included prospective cases with different outcomes as the following example cases show: Case A. Admission for FLTD-SCAR with SDC in hospital, prolonged or modified TB treatment and follow-up clinical information available 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.

(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 TB diagnosis was refuted, three went straight onto a modified regimen due to severity of organ involvement, and one did not undergo SDC for unknown reasons. Seventeen TB-SCAR patients had a positive reaction to ≥1 FLTD, with ten reacting to a single TB drug and seven to >1 FLTD.

3.3. 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 (Supplementary Table 3) showed no clear predictors of mortality. Additionally, 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%); $P = 0.171$)] and lower median (IQR) baseline CD4 count [72 (62–118) vs 109 (53–200) cells/uL; $P = 0.305$], but neither of these differences reached statistical significance. Median (IQR) peak eosinophil was also non-significantly higher in those who died [3.14 × 10^9/L (2.22–4.05 × 10^9/L) vs 1.05 x10^9/L (0.6–2.34 × 10^9/L); $P = 0.49$].

Table 2 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 s-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 full FLTD (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

Table 1
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%)

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.

[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.

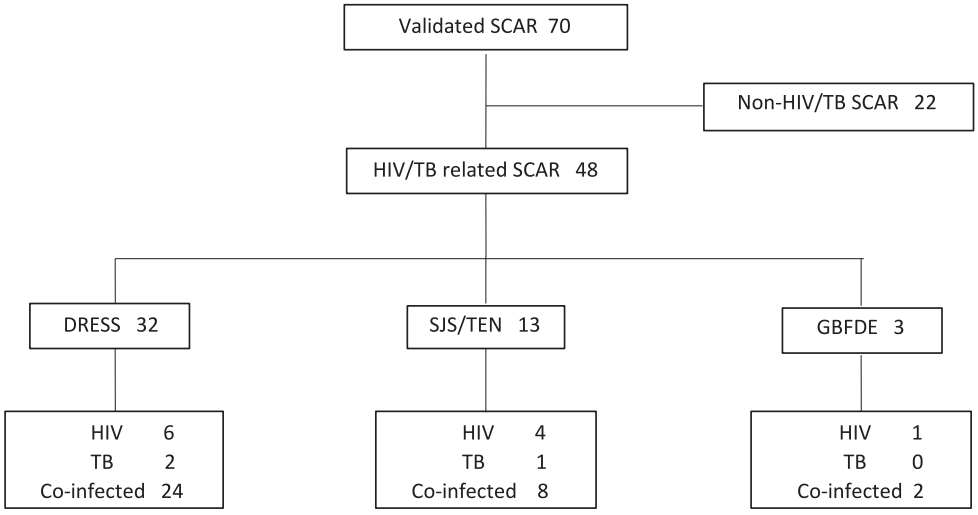

Fig. 1B. Flow diagram of included patients. Subclassification by SCAR phenotype with numbers of HIV, TB and co-infected in each SCAR phenotype. SCAR not related to HIV or TB treatment was not included. One patient had missing data and was admitted to another tertiary hospital and was therefore not included. 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.

due to a SCAR culprit drug in the initial ART regimen (two nevirapine, one tenofovir/efavirenz combination and one dolutegravir) and two unknowns. PLWH who remained in care post-SCAR admission showed increases in median (IQR) CD4 counts at 6- and 12-months (Fig. 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) vs 388 (314–605) cells/uL; $P = 0.1018$]. 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.

4. Discussion

Our study reports 6- and 12-month outcomes for the largest cohort of HIV and TB-associated SCAR reported to date, with >70% 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 ≥1 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-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 and patients with a CD4 cell

Table 2
Key outcomes of patients admitted with FLTD-associated SCAR.

	OVERALL48	DRESS32	SJS/TEN13	GBFDE3
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 showing specific TB and HIV outcomes with regards to treatment regimens at discharge, death, TB treatment success rates, and recurrence of TB.
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.
[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.

count <100 cells/uL have reported 6- and 12-month mortality of 6–25% [21,22]. Furthermore, a predominantly European review and survival analysis of SJS/TEN admissions, where HIV-infection was ±9%, showed mortality rates of up to 34% at one year [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 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 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, 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 modifying and lengthening TB treatment regimens in 80% of patients. Our unit has pioneered SDC to ensure that TB-SCAR patients, especially with associated HIV, are re-established timeously on as many FLTDs as possible [9]. In this cohort nearly two-fifths of TB-SCAR patients had ≥2 FLTDs included in their regimens after SCAR and seven patients recommenced all four FLTDs. This supports efforts to incorporate SDC for SCAR into national policy in high HIV/TB burden settings. Despite modification of TB regimens, 65% of SCAR patients had successful treatment outcomes. However, this is lower than SA studies that report TB treatment outcomes among TB patients in general (combined treatment completion and cure rates) which range from 70% to 82% and fall significantly short of the World Health Organization goal of 85% [21,26–28].

HIV care was also disrupted by SCAR admission, with one-fifth changing ART regimens within 12-months post-SCAR. Furthermore, we could not find any record of HIV care or ART for 12 post-SCAR patients, which may reflect death, movement out of the province, or ART interruption. However, if HIV patients remained in care, immune recovery, as measured by CD4 cell count, progressively improved in the 12-months post-SCAR. CD4 count improvement was slower over the first 6-months compared to national expected rates [199 (89–427) 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 SPV recording electronic clinical encounters and medication dispensing. Thus, we were unable to determine if patients were accessing care elsewhere, and we need to assume that dispensed medication equates to treatment adherence. Additionally, data capturing in some clinics may be incomplete accounting for some of the missing data. Generally, CD4 cell count data supports ART adherence, and the integrated coverage of SPV is well established [31]. The observational nature of this study and reliance on routine clinical care meant there was missing data, particular for VL, which are not regularly measured in primary care. Therefore, we have been cautious in our conclusions.

This is the largest study 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 impact of SCAR on HIV and TB treatment. Mortality, although high, was like other non-SCAR HIV/TB cohorts demonstrating that the management and SDC strategy used may have optimised these patients' outcomes. However, there remains a need to support ongoing research to improve prevention and treatment of SCAR amongst PLWH [32,33]. Additionally, prospective registry-related follow-ups and clinical review may help to further improve both short- and long-term outcomes and understanding of the natural history in these complex patients.

CRediT authorship contribution statement

S. Veenstra: Data curation, Formal analysis, Writing – original draft. **M.N. Porter:** Data curation, Formal analysis, Supervision, Writing – review & editing. **B.N. Thwala:** Data curation, Writing – review & editing. **N. Pillay:** Data curation, Writing – review & editing. **M.A. Panieri:** Data curation, Writing – review & editing. **J. van der Westhuizen:** Data curation, Writing – review & editing. **E.J. Phillips:** Writing – review & editing. **G. Meintjes:** Writing – review & editing. **S.**

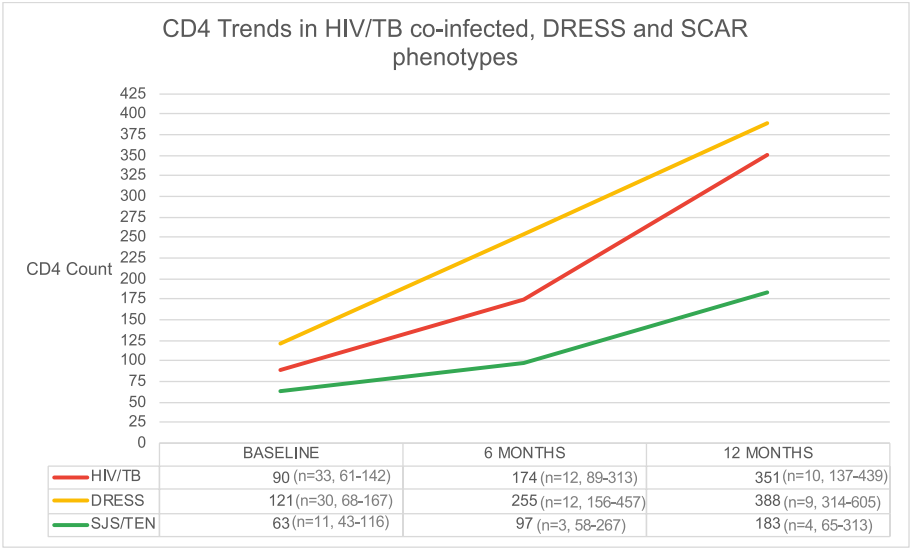

Fig. 2. CD4 trends over time in overall, HIV-associated TB, DRESS and SJS/TEN phenotypes. Median CD4 (cells/uL) counts at baseline, 6 months and 12 months for the overall cohort, co-infected subgroup and DRESS and SJS/TEN SCAR phenotypes. GFBDE CD4 trends were not included as there was limited CD4 information 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; SCAR, severe cutaneous adverse reaction; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; TB, tuberculosis.

Dlamini: Writing – review & editing. **R.J. Lehloenya:** Writing – review & editing. **J. Peter:** Supervision, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2023.100374.

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