Comparison of treatment outcome definitions in drug-resistant tuberculosis patients with high incidence of acquired second-line drug resistance

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Background. Simplified drug-resistant tuberculosis (DR-TB) treatment outcome definitions, mostly centred around receipt of treatment and sputum culture status at 6 months after treatment initiation, have been proposed, but have not been widely evaluated in resource-limited settings.
Objectives. To compare DR-TB treatment outcomes, as defined by the World Health Organization (WHO) at the time of treatment, with simplified definitions.
Methods. We performed retrospective folder reviews of a cohort of 246 South African DR-TB patients, most of whom developed second-line drug resistance. Sequential treatment outcomes were assigned retrospectively using both simplified Tuberculosis Network European Trials Group (TBNET)-based and 2013 WHO-based definitions.
Results. Of 246 patients, 40% were HIV-positive, and 88% developed second-line drug resistance. Patients were observed for a median of 38 (interquartile range 24 - 63) months from DR-TB treatment initiation. Using WHO-based definitions, 93% of patients had >1 sequential outcome, whereas with simplified definitions, 25% of patients had >1 outcome. Fewer outcomes of cure (3% v. 9%) and more outcomes of treatment failure (42% v. 22%) were assigned using simplified definitions.
Conclusion. Simplified outcome definitions applied to real-world patients with long, often complex treatment histories resulted in underestimating cures and overestimating treatment failures compared with WHO-based definitions. Simplified definitions may identify more individuals at higher risk for treatment failure than WHO-based definitions, but without consistent programmatic follow-up it may be difficult to distinguish cure, failure and loss to follow-up.

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Monitoring outcomes of drug-resistant tuberculosis (DR-TB) treatment is important in clinical practice and for surveillance. In 2006, the World Health Organization (WHO) first published standardised multidrug-resistant TB (MDR-TB) treatment outcome definitions, which were updated in 2008 and 2013.[1-3]

Since then, there have been several calls for revised definitions.[4] In 2016, the Tuberculosis Network European Trials Group (TBNET) proposed simplified treatment outcome definitions and compared them with WHO 2013 definitions in a cohort of 380 patients with DR-TB.[5] They demonstrated that treatment failure and cure were underestimated using WHO definitions, owing to a lack of sputum cultures obtained after the intensive phase of treatment, which could reflect limited access to healthcare or inability of patients to produce sputum late in therapy. Unlike WHO definitions, which depend largely on repeated culture status in relation to timing of intensive phase of treatment, simplified definitions rely on receipt of treatment and culture status at 6 months after treatment initiation,[6] and incorporate an observation period of 1 year after treatment completion to consider relapse-free cure. In 2019, Schwoebel *et al.*[7] assessed whether WHO 2013 definitions apply to shorter treatment regimens for MDR-TB in low- and middle-income countries, and proposed new definitions whereby treatment failure and cure were determined by culture status at ≥6 months instead of being tethered to the end of the intensive phase.

It is important that DR-TB treatment outcome definitions are standardised to facilitate comparability and guide policy-making. DR-TB patients observed over long durations in a programmatic setting can have complex treatment histories and, as a result, application of treatment outcome definitions poses a challenge.[8] We sought to determine whether application of simplified TBNET-based definitions to programmatic data

in a resource-limited setting would facilitate less complicated accounting of treatment outcomes than WHO-based definitions.

Methods

We performed retrospective medical record reviews of a cohort of South African (SA) adult DR-TB patients from the Western Cape Province. As the primary aim of the overarching study was to examine acquired resistance in patients with MDR-TB, we used National Health Laboratory Service data to identify DR-TB patients who had serial second-line drug susceptibility tests (DSTs) performed (primarily ofloxacin and amikacin) between 2008 and 2015. Second-line DSTs after the initial one are ordered by a patient's treating clinicians; additional DSTs are performed when patients are not improving clinically or if cultures do not convert by 6 months, suggesting concern for treatment failure and possible drug resistance. Of those identified with serial second-line DSTs, we included patients who were hospitalised at a specialised TB hospital (Brooklyn Chest Hospital in Cape Town) at any time before 30 June 2017 (study censor date). Detailed characteristics of this cohort of patients have been previously described.[9] We initially aimed to determine treatment outcomes using WHO 2013 definitions. However, due to challenges in interpretation of these definitions, we developed more detailed 'WHO-based' study definitions (Table 1). For example, WHO 2013 criteria for assigning outcomes of treatment failure and cure are determined by results of 'consecutive cultures taken at least 30 days apart'. In our setting, patients with DR-TB routinely have monthly sputum collections. If, however, these occurred for practical purposes every 4 weeks (28 days), the interval would not meet the required minimum time between sputa. For our study criteria, we therefore modified the minimum time between sputa to ≥23 days. In addition, WHO definitions do not stipulate a maximum time period between consecutive sputa, which means that in theory an acceptable time between consecutive sputa could be years apart and not be clinically meaningful. For our study criteria we stipulated a maximum period of ≤120 days between sputa.

Due to variability in the adherence to and prescribed duration of treatment with injectable agents, we adopted the WHO-recommended approach that the intensive phase of treatment be regarded as the first 8 months from treatment initiation, and the continuation phase as the period thereafter. WHO 2013 criteria define a patient as lost to follow-up (LTFU) if treatment is interrupted for ≥2 consecutive months. However, within the LTFU group, we distinguished between: those who interrupted treatment for ≥2 consecutive months and remained untraceable v. those who were traceable and either remained untreated or resumed treatment; those who were prescribed the same regimen for the same diagnosis when they resumed treatment v. those who were prescribed new regimens; and those who interrupted in the intensive phase v. continuation phase of treatment.

We applied and compared TBNET-based simplified outcomes with WHO-based treatment outcomes (defined in Table 1). To ensure we applied simplified definitions consistently, we corresponded with TBNET authors, who provided additional methodology details for their definitions. 'Month 6' was defined by TBNET as between day 154 and 182 after treatment initiation, while culture status at month 6 was defined by the latest culture result in this period. In our cohort, we expected that patients would have monthly programmatic sputum cultures. However, we suspected that the interval might be too narrow and could result in a high proportion of patients receiving undeclared outcomes. Therefore, for outcomes assigned as undeclared, we secondarily compared outcomes using an alternative 'month 6' interval, extended by an additional 28 days (i.e. 'month 6' was redefined as day 154 - 210 after treatment initiation). We considered the TBNET definition of 'Death during observation' and the WHO-based definition of death as death during or within 7 days of stopping treatment. Death superseded 6-month outcomes of treatment failure or undeclared outcome for TBNET-based and WHO-based definitions. We assigned outcomes of cure based on TBNET-based criteria of negative culture status 6 months after treatment initiation, no positive culture thereafter and no record of relapses within 1 year after treatment completion. However, in our setting, we expected that few patients would have clinical follow-up or sputum cultures performed after treatment completion, and we therefore evaluated secondarily whether cases of cure had culture results available within 1 year of treatment completion.

Using WHO-based definitions, patients can have multiple sequential outcomes if, for example, they have treatment failure that requires regimen changes, or have patient-initiated treatment interruptions of ≥2 months but then resume treatment. In TBNET's observational cohort, only one outcome, for a single treatment period, was assigned per patient. However, in our retrospective study of patients who received prolonged, often complex, programmatic care, consecutive simplified outcomes were assigned in certain cases. If a patient was considered LTFU at 6 months (received no treatment during month 6) but resumed treatment thereafter, an additional outcome was assigned for the subsequent treatment period. If treatment changed owing to new resistance data, but the patient remained on treatment, simplified definitions were applied independently of treatment changes by TBNET, and only one outcome was assigned. However, in our cohort, if a patient initiated a new regimen due to new resistance results after >60 days interruption without treatment, we assigned an additional TBNET-based outcome for the new treatment period (i.e. after treatment failure or undeclared outcomes).

We focused additional assessments on toxicity-related treatment failure according to WHO-based definitions, and we determined 24-month outcomes for patients who had treatment failure according to TBNET-based definitions. In addition to comparing WHO-based treatment outcomes with simplified TBNET-based outcomes, we also secondarily compared differences that arose from using WHO-based study criteria v. WHO 2013 criteria to assign sputum culture conversion and reversion events (Table 1).

Study data were managed using Research Electronic Data Capture.[10] Descriptive analyses were performed using Stata 14 (StataCorp, USA). Ethics approvals and waiver of informed consent were granted by the Vanderbilt University Institutional Review Board (ref. no. 131289) and the Human Research Ethics Committees at the University of Cape Town (ref. no. 614/2014) and Stellenbosch University (ref. no. N14/08/106). The study was approved by the Western Cape Department of Health and the City of Cape Town.

Results

Among 246 patients, 17% had second-line drug resistance (to fluoroquinolones and/or injectable drugs) at initial DR-TB diagnosis;

Table 1. Comparison of treatment outcomes definitions: TBNET-based simplified definitions v. WHO-based study definitions*

Measure	TBNET-based simplified definitions	WHO-based study definitions	WHO 2013 definitions
Cure	A negative culture status 6 months after treatment initiation, no positive culture thereafter, and no relapses within 1 year after treatment completion	Treatment completion, without evidence of treatment failure, and with at least three consecutive negative sputum cultures (**≥23 days apart**) after the intensive phase and without subsequent positive sputum cultures in the treatment period	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures **≥30 days apart** are negative after the intensive phase
Treatment completion	N/A	Completion of programmatic treatment, as recommended by the national TB programme, without evidence of treatment failure, but with no record of at least three consecutive negative sputum cultures (**≥23 days apart**) after the intensive phase (**if no specific documentation was available that the intended treatment course was completed, we regarded completion as a minimum treatment duration of 18 months**).	Treatment completed as recommended by the national policy without evidence of failure BUT no record that 3 or more consecutive cultures **≥30 days apart** are negative after the intensive phase
Death	Death during observation	Death, for any reason, while on TB treatment **or within ≤7 days of stopping treatment**. Death supersedes any other treatment outcome at that time point.	A patient who dies for any reason during the course of treatment
Treatment failure	A positive culture status 6 months after treatment initiation or thereafter, or a relapse within 1 year after treatment completion	Treatment terminated or the need for permanent regimen change of at least two anti-TB drugs because of: (*i*) lack of conversion by the end of the intensive phase, or (*ii*) bacteriological reversion in the continuation phase after conversion to negative, or (*iii*) evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or (*iv*) adverse drug reactions. **Treatment termination is provider-initiated and was defined as no new regimen starting within ≤7 days of drugs being stopped, whereas regimen change was defined as a new regimen starting within ≤7 days of drugs being changed/stopped.**	Treatment terminated or need for permanent regimen change of at least 2 anti-TB drugs because of: (*i*) lack of conversion by the end of the intensive phase, or (*ii*) bacteriological reversion in the continuation phase after conversion to negative, or (*iii*) evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or (*iv*) adverse drug reactions
Lost to follow-up	Non-receipt of care 6 months after treatment initiation	Treatment interruption for 2 consecutive months (>60 days), treatment not restarted and patient untraceable (**by hospital records or laboratory records**)	A patient whose treatment was interrupted for 2 consecutive months or more
Treatment interruption	N/A	**Patient-initiated cessation of treatment either: (*i*) treatment interruption for ≥2 consecutive months (>60 days) during the intensive or continuation phase; and the same treatment for the same diagnosis was not restarted, but the patient remained traceable by hospital records or laboratory records (same treatment was defined as all drugs in the regimen remained the same plus or minus one drug added or switched; a change from one fluoroquinolone to another was not counted towards the number of drugs changed/switched, nor was a change from kanamycin to amikacin or vice versa) OR (*ii*) treatment interruption for ≥2 consecutive months (>60 days) during the intensive phase, but the same treatment was resumed for the same diagnosis (i.e. early treatment stopped but resumed). (When such patients restarted treatment, it constituted a new treatment period. However, if treatment was interrupted for >60 days during the continuation phase but the same treatment was resumed for the same diagnosis, this was not assigned an outcome of treatment interruption, but was regarded as a continuous treatment period).**	N/A

...continued...

Table 1. (continued) Comparison of treatment outcomes definitions: TBNET-based simplified definitions v. WHO-based study definitions*

Measure	TBNET-based simplified definitions	WHO-based study definitions	WHO 2013 definitions
Not evaluated	An outcome that was not assessed was assigned as 'undeclared'; owing to transferral out of the cohort, no culture status available at 6 months while the patient was receiving care, or no post-treatment assessment	Unable to assign any of the options above. This included, but was not limited to, patients with missing clinical data, **patients with ongoing treatment (receiving treatment for TB at study censor date)** and patients who transferred out to another province for TB care.	A patient for whom no treatment outcome is assigned. This includes cases transferred out to another treatment unit and whose treatment outcome is unknown.
Sputum culture conversion and reversion	N/A	'Conversion' was defined as 2 consecutive negative sputum cultures, **≥23 days and ≤120 days apart**. The first negative culture date was used as the date of conversion. 'Lack of conversion' required ≥60 days of treatment and at least two positive cultures since the start of treatment. 'Reversion' was defined as two consecutive positive sputum cultures, after conversion, ≥23 days and ≤120 days apart. The first positive culture date following conversion was used as the date of reversion.	Culture is considered to have converted to negative when two consecutive cultures, **≥30 days apart**, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, **≥30 days apart**, are found to be positive. In such a case, the specimen collection date of the first positive culture is used as the date of reversion.

TBNET = Tuberculosis Network European Trials Group; WHO = World Health Organization; TB = tuberculosis.
*For reference purposes, WHO 2013 definitions are also shown, with differences between WHO 2013 and WHO-based study definitions in bold.

all others had resistance to rifampicin and isoniazid. At subsequent second-line testing, 88% of patients had developed additional second-line drug resistance.[9] Most patients received standardised DR-TB regimens, which included injectable agents.[11] Bedaquiline was generally unavailable, unless accessed on compassionate grounds or in clinical trials (9% of patients). Median observation, from the time of DR-TB treatment initiation until death or censor date, was 38 (interquartile range 24 - 63) months. HIV prevalence was 40%.

Using WHO-based definitions, 93% of patients had >1 sequential outcome assigned in total, whereas with TBNET-based definitions, 25% of patients had >1 sequential outcome (Table 2). Many patients experienced patient-initiated treatment interruptions of ≥2 months (47% overall), and 19% experienced >1 treatment interruption. Patients who had interruptions in the intensive phase or who initiated new regimens after interruptions generally commenced a new intensive phase, whereas those who had interruptions in the continuation phase and resumed the same treatment generally did not commence a new intensive phase. Interruptions contributed to a higher number of sequential outcomes assigned using WHO-based definitions. Similarly, regimen changes due to treatment failure increased the overall number of sequential outcomes assigned using WHO-based definitions, whereas with simplified definitions, a new outcome was not necessarily assigned if a regimen changed. Comparisons of DR-TB treatment outcomes using WHO-based v. TBNET-based definitions are shown in Table 3. Comparison of the most recent outcomes per patient showed fewer outcomes of cure (3% v. 9%), and more outcomes of treatment failure (42% v. 22%) were assigned using TBNET-based v. WHO-based definitions, whereas proportions were similar for death (33% v. 33%), LTFU (4% v. 4%) and unevaluated/undeclared outcomes (18% v. 17%; Fig. 1). The WHO-based outcome of treatment interruption (15%) can be considered an alternative/equivalent to the WHO 2013 LTFU category, thereby producing a higher proportion of LTFU using WHO-based v. TBNET-based definitions (19% v. 4%; Fig. 1). Further assessment of the high proportion of TBNET-based treatment failure (*n*=104, 42%) demonstrated that at 24 months after starting the most recent treatment, 15 (14%) had culture conversion (all were still on treatment) and the remainder were culture positive (*n*=49), had not had culture conversion (*n*=2), had died (*n*=15) or were LTFU (*n*=23).

Eight patients achieved cure using TBNET-based criteria of a negative culture status 6 months after treatment initiation, no positive culture thereafter and no documentation of relapses within 1 year after treatment completion. Secondary evaluation of the 8 cure cases demonstrated that 2 patients had culture results available within 1 year of treatment completion, thereby confirming a lack of relapse.

There was agreement between the two definitions of cure (TBNET-based v. WHO-based) in the most recent outcomes of 6 patients, whereas 2 patients with TBNET-based cure were allocated as unevaluated (insufficient clinical data), and 17 patients with WHO-based cure were assigned alternative outcomes (14 treatment failures and 3 undeclared outcomes) (Table 3).

Using WHO-based definitions, 3 patients had outcomes of treatment failure due to adverse drug reactions requiring regimen change, 2 died within 4 months of regimen change and 1 had an outcome of cure but died 3 months after cure.

Table 2. Number of DR-TB treatment outcomes per patient using simplified TBNET-based definitions v. WHO-based definitions (*N*=246)

Total DR-TB treatment outcomes assigned per patient, *n*	Simplified TBNET-based, *n* (%)	WHO-based, *n* (%)
1	184 (74.8)	18 (7.3)
2	47 (19.1)	101 (41.1)
3	13 (5.3)	73 (29.7)
4	1 (0.4)	32 (13.0)
≥5	1 (0.4)	22 (8.9)

DR-TB = drug-resistant tuberculosis; TBNET = Tuberculosis Network European Trials Group; WHO = World Health Organization.

Table 3. Comparison of DR-TB treatment outcomes using simplified TBNET-based definitions v. WHO-based definitions (*N*=246)

	TBNET-based simplified outcome					
WHO-based outcome	Cure, *n*	Treatment failure, *n*	LTFU, *n*	Death, *n*	Undeclared, *n*	Total, *n*
First DR-TB treatment outcome*						
Cure	2	2	0	0	2	6
Treatment completion	0	0	0	0	0	0
Treatment failure	1	69	1	29	19	119
LTFU	0	2	0	0	0	2
Treatment interruption	0	25	34	8	15	82
Death	0	0	0	20	0	20
Not evaluated	0	7	4	3	3	17
Total	3	105	39	60	39	246
Most recent DR-TB treatment outcome†						
Cure	6	14	0	0	3	23
Treatment completion	0	0	0	0	0	0
Treatment failure	0	39	0	0	14	53
LTFU	0	6	1	0	2	9
Treatment interruption	0	19	6	0	12	37
Death	0	0	0	82	0	82
Not evaluated	2	26	2	0	12	42
Total	8	104	9	82	43	246

DR-TB = drug-resistant tuberculosis; TBNET = Tuberculosis Network European Trials Group; WHO = World Health Organization; LTFU = lost to follow-up.
*First period when standardised DR-TB treatment was administered for a DR-TB diagnosis; monodrug-resistant TB. diagnoses and treatment outcomes were not evaluated.
†For patients who had only one outcome assigned in total, the first outcome is also presented as the most recent outcome.

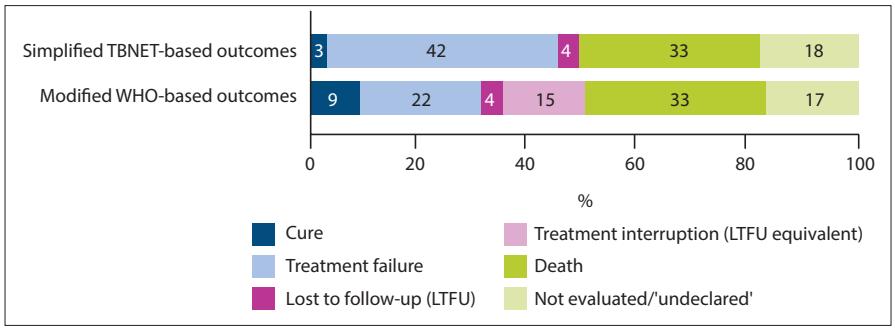

Fig. 1. Comparison of most recent drug-resistant tuberculosis treatment outcomes in 246 adult patients using simplified Tuberculosis Network European Trials Group (TBNET)-based definitions v. World Health Organization (WHO)-based definitions.

Overall, there were 53 treatment periods in 48 patients with undeclared outcomes by simplified criteria owing to lack of sputum culture results at 6 months (culture was either not performed or the sample was contaminated). When we re-evaluated outcomes in this subset using an alternative 6-month interval (widened by 28 days), alternative outcomes were assigned in 53% (25 undeclared outcomes were instead assigned as treatment failure and 3 as cure).

Using WHO-based criteria for conversion and reversion, 136 patients (55%) experienced sputum conversion. Of these, 112 (82%) experienced subsequent sputum reversion and 37 (27%) experienced >1 reversion after a conversion event. A comparison of sputum culture conversion/reversion events between WHO-based and WHO 2013 criteria demonstrated differences in 25 patients (10%). In 9 patients, the shortened minimum time between consecutive sputa using WHO-based criteria (≥23 v. ≥30 days) resulted in more conversion/reversion events, whereas in 2 patients the shortened maximum time between consecutive sputa (≤120 days v. no maximum time) resulted in fewer conversion/

reversion events. In the remaining 14 patients, the dates of conversion/reversion differed but not the total number of conversion/reversion events. The net result was 2 patients with different final assigned culture status (one net reversion and one net conversion).

Discussion

We found that the use of different DR-TB treatment outcome definitions resulted in substantial differences in the number of sequential treatment outcomes assigned, and determinations of cure, treatment failure and LTFU in a highly selected cohort of SA patients. The larger number of total sequential outcomes with WHO-based definitions was mostly due to: (*i*) regimen changes that triggered outcomes of treatment failure (whereas regimen changes did not trigger outcome assignment per simplified definitions); and (*ii*) patient-initiated treatment interruptions of ≥2 months that triggered outcomes of LTFU/treatment interruption (whereas non-receipt of treatment at 6 months after treatment initiation triggered outcomes of LTFU as per simplified definitions). Although this finding reflects the long and complicated treatment course of patients, comparison of the most recent outcome per patient is of primary interest in a programmatic context.

In contrast to TBNET's finding in a European observational cohort that WHO definitions underestimate cure,[5] we found fewer outcomes of cure were assigned using TBNET-based definitions. This was due to either lack of sputum culture results at 6 months after treatment initiation (TBNET: undeclared outcome) or positive culture results at ≥6 months after treatment initiation (TBNET: treatment failure), despite several such patients proceeding to treatment completion with ≥3 consecutive negative sputum cultures (WHO: cure). Furthermore, most patients did not have specific follow-up 1 year after treatment, preventing verification of relapse-free cure according to simplified definitions.

With the emphasis on any positive culture result at ≥6 months after treatment initiation, more outcomes of treatment failure were assigned using TBNET-based v. WHO-based definitions, as the definition is applied independently of subsequent sputum conversion (potential WHO-based cures) or missing clinical data (WHO-based unevaluated outcomes).

Based on our experience with applying different sets of definitions, specifying the number of days rather than using months and specifying window periods rather than fixed time points is preferable for defining the timing of culture data and outcome events, as it makes the interpretation of definitions less challenging and less susceptible to variation. TBNET-based definitions rely largely on sputum culture assessment during a 29-day interval at 6 months after treatment initiation. Widening the '6-month' interval from 29 days to 56 days resulted in 53% of undeclared outcomes receiving an alternative outcome, suggesting a wider interval is more practical when relying on programmatic sputum results. While TBNET-based definitions may be useful in research settings, they may not be as feasible in programmatic settings, particularly in patients with interrupted and/or prolonged treatment.

Our study had several limitations. First, we depended on clinical records with limits in treatment and follow-up data inherent in the retrospective design. Second, our findings are not generalisable to all patients with DR-TB since the patients were highly selected. Our study, however, provided an opportunity for comparison of definitions applied to severely ill patients under programmatic conditions. Third, our study patients mostly received older, injectable-based regimens that are being replaced by shorter regimens composed of all-oral drugs. In the context of changing treatment recommendations that have earlier treatment response thresholds and lack traditional intensive and continuation phases, several groups, including TBNET, have proposed revisions of WHO DR-TB treatment outcome definitions, culminating in a WHO meeting in 2020 to consider revising and simplifying the WHO 2013 definitions.[12] Our study illustrates that simplifying the WHO 2013 definitions may leave less room for interpretation and better accommodate variation in timing of sputum cultures and designation of conversion or reversion under programmatic conditions. Specifically, the anticipated WHO 2021 definitions for culture conversion and reversion do not reference intensive or continuation phases, and the minimum time required between consecutive sputum cultures is reduced from 30 days to 7. Additionally, the anticipated WHO 2021 definition for treatment failure no longer specifies that a minimum of two drugs in the regimen require changing (one is sufficient). Our study found that few patients had treatment failure due to adverse drug effects requiring two drug regimen changes, but decreasing the requirement to one drug change for toxicity may overestimate treatment failure for patients who effectively complete treatment after drug substitution. The advantage, however, is that it enables better reporting of toxicity-related data, which remains a priority for the WHO through compatible efforts such as the active TB drug-safety monitoring and management framework.[13] Our study highlights the paucity of programmatic assessment of sputum culture status after treatment completion, and the complexities caused by treatment interruptions that occur in programmatic conditions. Programmatic implementation of revised WHO definitions will allow further assessment of how simplified definitions allow useful reporting and comparability of DR-TB treatment outcomes.

Conclusion

Simplified outcome definitions applied in programmatic settings to SA patients with long, often complex treatment histories resulted in fewer outcomes of cure and LTFU, and more outcomes of treatment failure compared with WHO-based definitions. The ability to distinguish cure, treatment failure, and LTFU using simplified definitions may improve with consistent programmatic treatment and post-treatment follow-up.

Declaration. KD is a member of the *AJTCCM* editorial board. This manuscript was not given any priority over other manuscripts and was subjected to the same review process as any other. Another editor assumed responsibility for overseeing the peer review of this submission, and the author's editorial board member status had no bearing on editorial consideration and a final decision.

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Author contributions. Study design: YFvdH, EP and KA; data collection:

EP and KA; data analysis: KA and YFvdH; writing of manuscript draft: KA. All authors reviewed and approved the manuscript before submission.

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Conflicts of interest. None.

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