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Safety Profile of Updated Weight-based Anti-Tuberculosis Therapy Compared with Conventional Dosing Regimens during the Intensive Phase of Pulmonary Tuberculosis Treatment: A Retrospective Cohort Study

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ABSTRACT: The World Health Organization updated weight-based ATT dosing to optimize drug exposure, but safety evidence in Indonesian populations is limited. This study compared ADR incidence, severity, and timing between new and conventional regimens during intensive-phase pulmonary tuberculosis treatment. In a retrospective cohort of 112 newly diagnosed pulmonary tuberculosis patients at Dr. Wahidin Sudirohusodo Hospital and affiliated hospitals, Makassar, Indonesia, conventional (n=56) and new weight-based dosing (n=56) ATT regimens were compared. ADRs were assessed from medical records and the national tuberculosis information system. Chi-square/Fisher–Freeman–Halton tests and multivariate logistic regression analyzed ADRs and predictors. Baseline characteristics were comparable (all p>0.05). Gastrointestinal disturbances were most common, and most reactions occurred within the first two weeks. No significant differences in overall incidence, severity, or timing were observed. The updated regimen was not associated with overall adverse drug reactions (OR=0.90, 95% CI: 0.37–2.20; p=0.820) after multivariable adjustment (aOR=0.96, 95% CI: 0.38–2.45; p=0.938). Safety was comparable to conventional regimen. Further prospective multicenter studies are needed.

1. INTRODUCTION

Tuberculosis (TB) remains the leading cause of death from a single infectious agent worldwide, with an estimated 1.25 million deaths in 2023, including 161,000 among people living with HIV [1,2]. Despite the availability of effective treatment, TB continues to pose a major global public health challenge because treatment requires prolonged multidrug therapy, and unfavorable treatment outcomes remain common in routine clinical practice [3–5]. Successful TB control therefore depends not only on the efficacy of anti-tuberculosis therapy (ATT) but also on maintaining treatment adherence throughout the treatment course.

Standard first-line ATT consists of isoniazid, rifampicin, pyrazinamide, and ethambutol during the 2-month intensive phase, followed by isoniazid and rifampicin during the 4-month continuation phase [6]. Although highly effective, these drugs are

associated with a broad spectrum of adverse drug reactions (ADRs), ranging from mild gastrointestinal disturbances to severe hepatotoxicity, peripheral neuropathy, visual impairment, and cutaneous reactions [5,7,8]. Such adverse events may reduce treatment adherence, necessitate treatment interruption, and ultimately contribute to treatment failure and the emergence of drug resistance [7,8]. Among first-line anti-TB drugs, pyrazinamide, isoniazid, and rifampicin are associated with hepatotoxicity risk, with pyrazinamide carrying the highest risk [9,10]. Hepatotoxicity, characterized by elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), may present with abdominal pain, nausea, vomiting, and jaundice, and remains one of the most clinically significant complications of ATT because it may require treatment interruption or regimen modification [11,12]. Approximately 10% of patients receiving isoniazid develop elevated liver enzymes, while rifampicin may enhance isoniazid metabolism, increasing the production of hepatotoxic metabolites such as hydrazine [9,13].

To optimize drug exposure and improve treatment outcomes, the World Health Organization (WHO) recently updated its TB treatment recommendations by introducing revised weight-based dosing, including increased fixed-dose combination (FDC) tablet allocation for selected body weight categories [5,14]. Although these recommendations are expected to improve pharmacokinetic target attainment and therapeutic efficacy, concerns remain regarding whether increased drug exposure may also increase treatment-related toxicity in routine clinical practice. Adverse drug reactions are defined as noxious and unintended responses occurring at normal therapeutic doses and remain an important determinant of treatment adherence, treatment success, and the development of drug resistance when therapy is interrupted prematurely [1,2].

The occurrence of ATT-related adverse effects is multifactorial. Established risk factors include older age, sex, nutritional status, alcohol consumption, diabetes mellitus, HIV infection, and pre-existing liver disease [15,16]. In addition, pharmacogenetic variations involving N-acetyltransferase 2 (NAT2), cytochrome P450 2E1 (CYP2E1), and glutathione S-transferase (GST) substantially influence drug metabolism and individual susceptibility to hepatotoxicity [17–23]. However, most previous studies evaluating ATT-related toxicity have focused primarily on hepatotoxicity rather than the overall spectrum of adverse drug reactions associated with updated weight-based dosing strategies [8,9]. Furthermore, few studies have directly compared the safety profiles of updated WHO weight-based dosing and conventional dosing regimens in routine clinical practice, and real-world evidence regarding the safety implications of these dose modifications, particularly in Indonesian populations, remains limited. Therefore, this study aimed to compare the incidence, severity, and timing of adverse drug reactions between updated weight-based and conventional ATT dosing regimens during the intensive phase of pulmonary tuberculosis treatment, thereby providing evidence to support the optimization of treatment safety in routine clinical practice.

2. MATERIALS AND METHODS

2.1 Study design, setting, and population

This retrospective comparative cohort study was conducted at Dr. Wahidin Sudirohusodo General Hospital, Makassar, and its affiliated network hospitals from 1 March 2025 to 30 March 2026. The study population included all newly diagnosed pulmonary tuberculosis patients receiving intensive-phase ATT. The accessible population consisted of patients treated at the study sites during the defined study period.

2.2 Sample size and sampling technique

All eligible patients fulfilling the inclusion criteria were included using a total sampling technique. Participants were allocated into two groups according to treatment regimen, consisting of a conventional dosing group and a new weight-based dosing group, with equal allocation to ensure comparability. Sample size was calculated using a two-proportion comparison formula with a two-sided significance level of 0.05 and 80% statistical power. The calculation assumed an adverse drug reaction incidence of 5% in the conventional dosing group and 24.7% in the updated weight-based dosing group, based on previously published data evaluating ATT-related adverse events (Author et al., Year). Accordingly, the minimum required sample size was 50 patients per group. After allowing for a 10% incomplete data rate, 56 patients were included in each group.

2.3 Eligibility criteria

Patients were included if they were aged 18 years or older, newly diagnosed with pulmonary tuberculosis, and receiving intensive-phase ATT using either the conventional or new dosing regimen, with complete medical records available for all study variables. Patients were excluded if they had previous exposure to anti-tuberculosis therapy, incomplete medical records or

treatment documentation, or received concurrent hepatotoxic medications during the intensive phase that could interfere with the assessment of adverse drug reactions.

2.4 Variables and operational definitions

The independent variable was the ATT dosing regimen, categorized as conventional or new weight-based dosing. The primary outcomes were the incidence and severity of ADRs, including both clinical manifestations and laboratory abnormalities involving ALT, AST, bilirubin, urea, and creatinine. Potential confounders included age, sex, nutritional status, comorbidities such as diabetes mellitus, hypertension, and HIV infection, alcohol consumption, and other clinically relevant factors.

Pulmonary tuberculosis was defined as a case confirmed by clinical, microbiological, radiological, or histopathological evidence of Mycobacterium tuberculosis infection in patients receiving intensive-phase treatment (months 1–2). Drug-induced hepatitis was defined as elevation of ALT or AST ≥3 times the upper limit of normal (ULN) accompanied by symptoms such as abdominal pain, nausea, vomiting, fatigue, or jaundice, or ≥5 times the ULN in the absence of symptoms during ATT, as diagnosed by a pulmonologist. Baseline liver function test results obtained before ATT initiation were reviewed for all patients using the respective hospital laboratory reference ranges to distinguish pre-existing liver abnormalities from treatment-emergent drug-induced hepatitis. Non-hepatic ADRs included peripheral neuropathy, optic neuritis, gastrointestinal symptoms, and cutaneous reactions, defined based on clinical presentation and drug exposure profiles. ADR severity was classified according to WHO criteria and Common Terminology Criteria for Adverse Events (CTCAE) into mild, moderate, and severe categories. Mild gastrointestinal symptoms and other non-serious adverse events were recorded as ADRs only when documented by treating healthcare providers in the medical records and considered related to ATT according to the predefined study criteria. All suspected ADRs were reviewed and classified by pulmonologists according to these predefined diagnostic and severity criteria.

2.5 Data collection procedure and instruments

Data were obtained through systematic review of medical records and the national tuberculosis information system (SITB). Extracted variables included demographic characteristics, treatment regimen, clinical manifestations of ADRs, laboratory findings, and relevant comorbidities. Data were recorded using a standardized structured extraction form developed based on study variables and operational definitions. ADR severity classification was incorporated into the instrument to ensure uniform data categorization. All data were coded, anonymized, and entered into a master dataset for analysis.

2.6 Data management and statistical analysis

Data processing was performed using Microsoft Excel and analyzed using IBM SPSS Statistics software. Data management included editing, coding, tabulation, and cleaning to ensure completeness and consistency. Only patients with complete data for all study variables were included in the final analysis; therefore, no imputation for missing data was performed. Continuous variables, where applicable, were assessed for normality using the Shapiro–Wilk test prior to analysis. Univariate analysis was used to describe baseline characteristics, while bivariate analysis was performed using the Chi-square test or Fisher–Freeman–Halton exact test, as appropriate, to compare adverse drug reaction incidence between treatment groups. Multivariable logistic regression analysis was conducted to identify independent predictors of adverse drug reactions after adjustment for potential confounders. Multicollinearity among independent variables was assessed using variance inflation factors (VIF) before model fitting. Statistical significance was defined as a two-sided p-value <0.05.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics of Study Subjects

This study included 112 patients with newly diagnosed pulmonary tuberculosis receiving intensive-phase anti-tuberculosis therapy, equally divided into the conventional and updated weight-based dosing groups (n = 56 each). Baseline demographic and clinical characteristics were comparable between the two groups (Table 1). No statistically significant differences were observed in age, sex, comorbidities, radiographic findings, or tuberculosis diagnostic classification (all $p > 0.05$), indicating good baseline comparability for subsequent outcome analyses.

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Table 1. Baseline Characteristics of the Study Participants

Variable	Conventional Regimen, n (%)	New Dosing Regimen, n (%)	p-value
Age			**0.520**
<50 years	34 (60.7)	31 (55.4)	
≥50 years	22 (39.3)	25 (44.6)	
Sex			**0.450**
Male	26 (46.4)	28 (50.0)	
Female	30 (53.6)	28 (50.0)	
Comorbidities			
HIV infection	3 (5.4)	5 (8.9)	0.716
Diabetes mellitus	13 (23.2)	8 (14.3)	0.226
Hypertension	13 (23.2)	6 (10.7)	0.078
Alcohol consumption	10 (17.9)	5 (8.9)	0.165
History of liver disease	5 (8.9)	8 (14.3)	0.376
Chronic kidney disease (CKD)	4 (7.1)	5 (8.9)	1.000
Pleural effusion	12 (21.4)	11 (19.6)	0.815
Chest radiographic findings			**0.850**
Minimal lesion	25 (44.6)	26 (46.4)	
Extensive lesion	31 (55.4)	30 (53.6)	
Tuberculosis diagnosis			**0.690**
Bacteriologically confirmed	38 (67.8)	36 (64.3)	
Clinically diagnosed	18 (32.2)	20 (35.7)	

Data are presented as n (%). P-values were calculated using the Chi-square test. As shown in Table 2, body weight distribution was comparable between the conventional and updated weight-based dosing groups across all weight categories ($p = 0.45$). Differences in fixed-dose combination (FDC) tablet allocation reflected the updated WHO weight-based dosing recommendations rather than differences in baseline body weight distribution, supporting treatment-group comparability.

Table 1. Distribution of Body Weight Categories and Fixed-Dose Combination (FDC) Tablet Allocation According to Treatment Regimen

Body Weight Category	Conventional Regimen (FDC Tablets)	New Dosing Regimen (FDC Tablets)	Conventional, n (%)	New Dosing, n (%)	p-value
<30 kg	2 tablets	2 tablets	5 (8.9)	5 (8.9)	0.45
30–34 kg	2 tablets	3 tablets	10 (17.9)	12 (21.4)	
35–37 kg	2 tablets	4 tablets	8 (14.3)	10 (17.9)	
38–54 kg	3 tablets	4 tablets	18 (32.1)	17 (30.4)	

55–64 kg	4 tablets	4 tablets	10 (17.9)	9 (16.1)	
≥65 kg	4 tablets	5 tablets	5 (8.9)	3 (5.4)	

Data are presented as **n (%)**. P-value was calculated using the **Fisher–Freeman–Halton exact test**.

3.2 Incidence and Severity of Anti-Tuberculosis Drug Adverse Effects

This section examines the incidence and severity of ADRs during the intensive phase of anti-tuberculosis therapy, comparing conventional and new dosing regimens (Table 3). Gastrointestinal disturbances were the most frequently documented ADR in both treatment groups, with most cases classified as mild to moderate in severity. In the conventional group, 64.3% of participants were asymptomatic, while 14.3%, 17.8%, and 3.6% experienced mild, moderate, and severe symptoms, respectively. In the new dosing group, 62.5% were asymptomatic, with 21.4%, 10.7%, and 5.4% experiencing mild, moderate, and severe symptoms, respectively (p = 0.569). Peripheral neuropathy was absent in 91.2% of the conventional group and 89.2% of the new dosing group. Mild, moderate, and severe cases were observed in 5.3%, 3.6%, and 0% of the conventional group, compared to 7.1%, 1.8%, and 1.8% in the new dosing group (p = 0.685). Visual disturbances were rare. In the conventional group, 89.2% were asymptomatic, with 7.1% experiencing mild and 3.6% moderate impairment. In the new dosing group, 94.6% were asymptomatic, with 3.6% experiencing mild and 1.8% moderate impairment (p = 0.780). Pruritus was observed in a minority of cases. In the conventional group, 75.0% were asymptomatic, with 12.5%, 5.3%, and 7.1% experiencing mild, moderate, and severe pruritus, respectively. In the new dosing group, 80.4% were asymptomatic, with 8.9%, 5.3%, and 5.3% experiencing mild, moderate, and severe pruritus, respectively (p = 0.901). The distribution of drug-induced hepatitis (DIH) was similar between groups. In the conventional group, 64.3% had no DIH, with 17.8%, 10.7%, and 7.1% experiencing mild, moderate, and severe DIH, respectively. In the new dosing group, 58.9% had no DIH, with 21.4%, 16.1%, and 3.6% experiencing mild, moderate, and severe DIH, respectively (p = 0.664). Overall, no significant differences in the incidence or severity of ADRs were observed between the regimens during the intensive phase of treatment.

Table 2. Distribution of the Type and Severity of Adverse Drug Reactions According to Anti-Tuberculosis Treatment Regimen

Adverse Drug Reaction	***Conventional Regimen**				***New Dosing Regimen**				**p-value**
	None	**Mild**	**Moderate**	**Severe**	**None**	**Mild**	**Moderate**	**Severe**	
Gastrointestinal disturbances	36 (64.3%)	8 (14.3%)	10 (17.8%)	2 (3.6%)	35 (62.5%)	12 (21.4%)	6 (10.7%)	3 (5.4%)	0.569
Peripheral neuropathy	51 (91.2%)	3 (5.3%)	2 (3.6%)	0 (0.0%)	50 (89.2%)	4 (7.1%)	1 (1.8%)	1 (1.8%)	0.685
Visual disturbances	50 (89.2%)	4 (7.1%)	2 (3.6%)	0 (0.0%)	53 (94.6%)	2 (3.6%)	1 (1.8%)	0 (0.0%)	0.780
Pruritus	42 (75.0%)	7 (12.5%)	3 (5.3%)	4 (7.1%)	45 (80.4%)	5 (8.9%)	3 (5.3%)	3 (5.3%)	0.901
Drug-induced hepatitis (DIH)	36 (64.3%)	10 (17.8%)	6 (10.7%)	4 (7.1%)	33 (58.9%)	12 (21.4%)	9 (16.1%)	2 (3.6%)	0.664

Data are presented as **n (%)**. P-values were calculated using the **Chi-square test**.

3.3 Timing of Adverse Drug Reactions

Table 4 illustrates the distribution of the time to onset of ADRs during the intensive phase of anti-tuberculosis therapy. The timing of ADR occurrence exhibited a similar pattern between the conventional and new dosing groups. In both groups, the highest proportion of ADRs occurred within the first two weeks of treatment, with 25.0% of patients in each group experiencing early-onset reactions (≤2 weeks). This suggests that a significant proportion of adverse events emerged during the early phase of therapy. During weeks 3–4, ADRs were observed in 19.6% of patients in both the conventional and new dosing groups. In

weeks 5–8, ADRs were reported in 17.9% of the conventional group and 12.5% of the new dosing group, while late-onset events (>8 weeks) were noted in 16.1% and 19.6% of patients, respectively. The proportion of patients who did not experience any ADR during the intensive phase was also similar between groups, with 21.4% in the conventional group and 23.2% in the new dosing group. No statistically significant difference was found in the distribution of ADR onset timing between the two regimens (p = 0.943). These findings suggest that the new dosing regimen does not significantly alter the temporal pattern of adverse drug reactions compared to the conventional regimen.

Table 3. Time to Onset of Adverse Drug Reactions During Anti-Tuberculosis Therapy

Time to Onset	Conventional Regimen, n (%)	New Dosing Regimen, n (%)	p-value
≤2 weeks	14 (25.0)	14 (25.0)	0.943
3–4 weeks	11 (19.6)	11 (19.6)	
5–8 weeks	10 (17.9)	7 (12.5)	
>8 weeks	9 (16.1)	11 (19.6)	
No adverse drug reactions	12 (21.4)	13 (23.2)	
Total	**56 (100)**	**56 (100)**	

Data are presented as **n (%)**. P-values were calculated using the **Chi-square test** or **Fisher–Freeman–Halton exact test**, as appropriate.

3.4 Association Between Anti-Tuberculosis Drug Regimen and Adverse Drug Reactions

Table 5 illustrates the relationship between ATT dosing regimens and the incidence of ADRs during the intensive treatment phase. The proportion of patients experiencing ADRs was similar across the groups. In the conventional dosing group, 44 patients (78.6%) experienced at least one ADR, whereas 12 patients (21.4%) did not experience any adverse events. In the new dosing group, 43 patients (76.8%) reported ADRs, while 13 patients (23.2%) did not report any adverse events. Using the conventional regimen as the reference category (OR = 1.00), the new dosing regimen exhibited an odds ratio (OR) of 0.90 (95% CI: 0.37–2.20), suggesting a marginally lower, yet statistically insignificant, likelihood of ADR occurrence. The confidence interval included unity, indicating no significant association. Chi-square analysis corroborated the lack of a statistically significant relationship between dosing regimen and ADR occurrence (p = 0.820). Similarly, binary logistic regression analysis yielded consistent results, showing that the new dosing regimen was not significantly associated with either an increased or decreased risk of ADRs compared to the conventional regimen. In summary, these findings suggest that the safety profile of the new weight-based dosing regimen is comparable to that of the conventional regimen concerning the overall incidence of adverse drug reactions during the intensive phase of tuberculosis treatment.

Table 4. Association Between Conventional and New Anti-Tuberculosis Treatment Regimens and the Occurrence of Adverse Drug Reactions

ATT Regimen	No Adverse Drug Reactions	Adverse Drug Reactions	Total	OR	95% CI	p-value
Conventional dosing regimen	12 (21.4%)	44 (78.6%)	56 (100%)	1.00	Reference	0.820
New dosing regimen	13 (23.2%)	43 (76.8%)	56 (100%)	0.90	0.37–2.20	

Data are presented as **n (%)**. P-value was calculated using the **Chi-square test**. OR, odds ratio; CI, confidence interval.

3.5 Multivariate Analysis of Factors Associated with Adverse Drug Reactions

Table 6 displays the outcomes of a multivariate logistic regression analysis evaluating independent factors linked to ADRs during the intensive phase of anti-tuberculosis therapy. The model incorporated variables such as dosing regimen, age ≥50 years, poor nutritional status, alcohol consumption, history of liver disease, and extensive pulmonary lesions. Overall, none of these variables exhibited a statistically significant association with the occurrence of ADRs. The new dosing regimen yielded an

adjusted odds ratio (aOR) of 0.96 (95% CI: 0.38–2.45; p = 0.938), suggesting a risk of ADRs comparable to the conventional regimen after adjusting for confounding factors. Age ≥50 years was linked to a reduced but non-significant risk of ADRs (aOR = 0.55; 95% CI: 0.21–1.41; p = 0.214). Alcohol consumption indicated a non-significant increased risk of ADRs (aOR = 2.22; 95% CI: 0.45–10.95; p = 0.329), although the wide confidence interval reflected considerable uncertainty. Similarly, a history of liver disease was not significantly associated with ADR occurrence (aOR = 0.62; 95% CI: 0.16–2.33; p = 0.478). Extensive pulmonary lesions showed a tendency towards higher odds of ADRs (aOR = 2.11; 95% CI: 0.83–5.37; p = 0.117), yet this association did not achieve statistical significance. In conclusion, the multivariate analysis revealed that none of the assessed clinical or treatment-related factors, including the dosing regimen, were independently associated with adverse drug reactions during the intensive phase of tuberculosis treatment.

Table 5. Multivariate Logistic Regression Analysis of Factors Associated with Adverse Drug Reactions During Anti-Tuberculosis Therapy

Variable	Adjusted Odds Ratio (aOR)	95% CI	p-value
New dosing regimen	0.96	0.38–2.45	0.938
Age ≥50 years	0.55	0.21–1.41	0.214
Alcohol consumption	2.22	0.45–10.95	0.329
History of liver disease	0.62	0.16–2.33	0.478
Extensive pulmonary lesions	2.11	0.83–5.37	0.117

Data were analyzed using **multivariate logistic regression**. aOR, adjusted odds ratio; CI, confidence interval.

3.6 Discussion

The present study demonstrated that the updated weight-based ATT regimen exhibited a safety profile comparable to that of the conventional regimen during the intensive phase of pulmonary tuberculosis treatment. No significant differences were observed in the incidence, severity, or timing of ADRs between the two treatment groups, and the updated dosing strategy was not independently associated with an increased risk of ADRs after adjustment for potential confounders. Furthermore, both groups were comparable in terms of baseline demographic and clinical characteristics, minimizing the likelihood that differences in patient characteristics influenced the observed safety outcomes. These findings suggest that implementation of the updated WHO weight-based dosing recommendations does not appear to increase treatment-related toxicity in routine clinical practice.

Our findings are consistent with previous studies demonstrating that ATT-related toxicity is influenced predominantly by patient-related factors rather than by standard therapeutic dosing. Molla et al. (2021) reported that advanced age was no longer significantly associated with hepatotoxicity after adjustment for other clinical risk factors, while Zhao et al. (2020) similarly found no independent association between standard ATT dosing regimens and treatment-related toxicity after accounting for potential confounders [1,8]. Likewise, although comparable distributions of HIV infection, diabetes mellitus, chronic liver disease, chronic kidney disease, alcohol consumption, and other baseline characteristics were observed between the two groups in the present study, none appeared to substantially influence the comparative safety outcomes. These findings further support the interpretation that the observed similarity in ADR occurrence reflects comparable treatment safety rather than differences in baseline patient characteristics.

The biological plausibility of these findings is supported by the pharmacokinetic rationale underlying the updated WHO recommendations [14]. Weight-based dosing aims to achieve adequate plasma drug exposure and prevent subtherapeutic drug concentrations that may contribute to treatment failure and the emergence of drug resistance [5,14]. Rather than substantially increasing systemic drug exposure beyond the therapeutic range, the revised dosing strategy seeks to reduce interindividual variability in drug concentrations across different body weight categories. Consequently, optimized weight-based dosing would not necessarily be expected to increase treatment-related toxicity when administered within recommended therapeutic ranges. Similarly, although the updated WHO recommendations increase the number of FDC tablets for selected body weight categories, our findings suggest that increasing FDC tablet numbers according to body weight does not necessarily translate into increased toxicity. This observation is consistent with previous studies showing that weight-adjusted FDC formulations

improve dosing accuracy while maintaining acceptable tolerability [14,24]. Instead, the higher tablet allocation appears to represent pharmacologically appropriate dose optimization rather than excessive drug exposure.

The comparable incidence and severity of gastrointestinal disturbances, peripheral neuropathy, visual impairment, pruritus, and DIH observed between treatment groups further support previous evidence indicating that host-related factors play a more important role than modest dose adjustments in determining ATT-related toxicity [1,8]. Drug-induced hepatitis remains one of the most clinically important complications of first-line ATT because it may necessitate treatment interruption, regimen modification, and prolonged therapy. Although mild and moderate DIH occurred numerically more frequently in the updated dosing group, severe DIH was slightly more common in the conventional group, and these differences were not statistically significant. This observation is biologically plausible because ATT-induced hepatotoxicity is largely determined by individual susceptibility rather than modest differences in drug dosage. Reactive metabolites generated during the metabolism of isoniazid, rifampicin, and pyrazinamide, together with host pharmacogenetic variability involving NAT2, CYP2E1, and GST, have been recognized as the principal mechanisms underlying susceptibility to liver injury.

Another important finding was that most ADRs occurred within the first two weeks of treatment regardless of the dosing regimen. This temporal pattern is consistent with previous reports by Patterson et al. (2021) and Abbara et al. (2017), who demonstrated that ATT-related liver injury and other adverse reactions occur predominantly during the early weeks of treatment [25,26]. The absence of differences in ADR onset between treatment groups indicates that the updated dosing regimen does not alter the temporal pattern of toxicity. Therefore, careful clinical assessment and laboratory monitoring during the initial weeks of therapy remain essential irrespective of the dosing strategy.

Multivariable logistic regression further confirmed that the updated weight-based dosing regimen was not independently associated with ADR occurrence after adjustment for age, alcohol consumption, history of liver disease, nutritional status, and the extent of pulmonary lesions. Although alcohol consumption and extensive pulmonary involvement tended to increase the risk of ADRs, neither variable reached statistical significance. These findings are consistent with previous reports indicating that alcohol use and pre-existing liver disease contribute to hepatotoxicity risk, although their independent effects become less pronounced after adjustment for multiple clinical confounders [1,8]. Likewise, the lack of an independent association between extensive pulmonary lesions and ADR occurrence is in agreement with the findings reported by Mukura and Ruenwilai (2025) [9].

The present study has several important clinical implications. First, the updated weight-based ATT regimen appears to maintain a safety profile comparable to that of the conventional regimen despite increasing the number of FDC tablets in selected body weight categories. These findings provide reassurance for clinicians implementing the updated WHO dosing recommendations in routine practice, suggesting that concerns regarding increased tablet numbers should not necessarily discourage adoption of the revised dosing strategy. Second, because most ADRs occurred during the first two weeks of therapy, early clinical assessment and laboratory monitoring remain essential regardless of the dosing regimen used. Finally, the present findings further emphasize that patient-related factors, rather than dose adjustment alone, remain the principal determinants of ATT-related adverse events.

Future prospective multicenter studies with larger sample sizes, standardized ADR surveillance, pharmacokinetic measurements, and pharmacogenetic evaluation are warranted to validate these findings and better characterize individual susceptibility to ATT-associated toxicity. Such studies may further clarify the relationship between optimized weight-based dosing, systemic drug exposure, treatment tolerability, and long-term clinical outcomes.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective cohort design relied on existing medical records, limiting control over potential confounding factors and introducing the possibility of incomplete or inaccurate documentation. Consequently, mild or subjective adverse drug reactions (ADRs), particularly gastrointestinal symptoms or peripheral neuropathy, may have been underreported. Second, the analysis was restricted to the intensive phase of anti-tuberculosis treatment. Therefore, ADRs occurring during the continuation phase, including late-onset toxicities, were not evaluated, limiting assessment of the long-term safety profile of the treatment regimens. Third, medication adherence and treatment interruption were not evaluated. Because adherence may be influenced by treatment-related adverse effects and may also affect subsequent clinical outcomes, the absence of these data limits interpretation of the relationship between dosing strategy and treatment effectiveness. Fourth, pharmacogenetic factors known to influence anti-tuberculosis

drug metabolism, including polymorphisms in *N*-acetyltransferase 2 (NAT2) and cytochrome P450 2E1 (CYP2E1), were not assessed. These genetic variations may modify individual susceptibility to hepatotoxicity and other ADRs, potentially contributing to residual confounding. Fifth, pharmacokinetic parameters, including plasma drug concentrations, were unavailable; therefore, the relationship between dose adjustment, systemic drug exposure, and treatment-related toxicity could not be directly evaluated. Finally, this was a single-center study with a relatively modest sample size, which may limit the generalizability of the findings to other populations and healthcare settings. Future prospective multicenter studies incorporating standardized ADR surveillance, pharmacokinetic measurements, pharmacogenetic evaluation, and medication adherence assessment are warranted to validate these findings.

4. CONCLUSION

Updated weight-based ATT dosing demonstrated a safety profile comparable to that of conventional dosing during the intensive phase of pulmonary tuberculosis treatment. No significant differences were observed in the incidence, severity, or timing of adverse drug reactions between the two dosing strategies. These findings suggest that increasing fixed-dose combination (FDC) tablet allocation according to body weight does not appear to increase the observed risk of treatment-related adverse drug reactions. Nevertheless, early clinical and laboratory monitoring remains essential, particularly during the first weeks of therapy. Further prospective multicenter studies incorporating pharmacokinetic and pharmacogenetic evaluations are warranted to confirm these findings and further characterize the relationship between weight-based dose optimization and treatment-related toxicity.

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AUTHOR CONTRIBUTIONS

NYP conceived the study, collected data, performed the statistical analysis, interpreted the results, and drafted the manuscript. ID and HAP supervised the study, contributed to the study design, interpreted the findings, and critically revised the manuscript. JM, SN, and EA contributed to data interpretation, manuscript revision, and approved the final version of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (No. 214/UN4.6.4.5.31/PP36/2026). Institutional permission was granted by Dr. Wahidin Sudirohusodo General Hospital. Patient confidentiality was strictly maintained through anonymization of data, and the study was conducted in accordance with the Declaration of Helsinki principles.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Data are not publicly available because they contain information that could compromise participant confidentiality.

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