International Journal of Education, Vocational and Social Science
https://e-journal.citakonsulindo.or.id/index.php/IJEVSS
E-ISSN : 2963 4954
IJEVSS

The Relationship of Treatment History, Medication Adherence, and Anti-Tuberculosis Drug Side Effects with Drug-Resistant Tuberculosis: A Structured Narrative Review

Dhimaz Ralina Alghivary
Public Health Study Program, Epidemiology, Universitas Muhammadiyah Pontianak, West Kalimantan, Indonesia
Eka Hariani
Public Health Study Program, Epidemiology, Universitas Muhammadiyah Pontianak, West Kalimantan, Indonesia

Corresponding Author: Dhimazralinaa@gmail.com

Abstract

Drug-resistant tuberculosis (DR-TB) is a major challenge in TB control in Indonesia. This structured narrative review maps evidence on prior treatment history, medication adherence, and adverse effects of anti-tuberculosis drugs (ATD), distinguishing direct evidence on DR-TB from indirect evidence on treatment experience and adherence. A structured search of Google Scholar, Portal Garuda, PubMed, and institutional repositories was conducted for Indonesian- and English-language publications from 2020 to 2026. The initial search identified 668 records; twelve sources were retained in the narrative corpus, while six studies with sufficiently extractable findings are presented in the expanded characteristics table. Reported odds ratios (ORs) for prior treatment history ranged from 2.4 to 8.0 in cited observational studies, but confidence intervals were not consistently available and estimates were not pooled. Evidence linking adverse effects with non-adherence was indirect, and the available material did not establish mediation, temporal sequence, or a universal causal pathway to DR-TB. Acquired and transmitted resistance are discussed separately. The proposed three-factor relationship is retained only as a conceptual synthesis for future prospective research.

Keywords: adherence to medication; drug-resistant tuberculosis; literature review; side effects of anti-tuberculosis drugs; TB treatment history

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

INTRODUCTION

Tuberculosis (TB) remains one of the most serious public health problems at the global level. Based on the Global Tuberculosis Report 2025, an estimated 10.7 million new TB cases were recorded worldwide in 2024, with Indonesia occupying the second position among the largest contributors to the case burden after India (around 10% of global cases). The challenge of TB control has become increasingly complex with the emergence of a subpopulation of patients experiencing resistance to first-line anti-tuberculosis drugs, or drug-resistant tuberculosis (DR-TB). In 2024, an estimated 390,000 new cases of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) occurred globally, yet only 42% of them successfully accessed adequate therapy (World Health Organization, 2025).

DR-TB can emerge through more than one process. Acquired resistance can develop when the bacterial population is exposed to inadequate drug pressure, for example due to an unsuitable regimen, impaired absorption, drug interactions, or incomplete treatment. On the other hand, transmitted resistance occurs when a person is infected by a strain that is already resistant from the outset. Because these two processes cannot be distinguished from a cross-sectional design or the secondary data summarized in this review alone, non-adherence should not be regarded as a universal cause of DR-TB.

Prior treatment history, recurrent TB episodes, the regimen used, access to services, and strain characteristics may be related to resistance status, but the direction and mechanism of the relationship must be interpreted with caution. The side effects of anti-tuberculosis drugs may also be influenced by the regimen and disease severity, so they do not automatically precede DR-TB.

Although these three factors have been widely studied, the majority of prior literature has examined them separately and partially. Some studies limit their focus to treatment history as a single predictor, other studies examine adherence only in relation to general sputum conversion success without linking it to resistance, and another group of studies place the side effects of anti-tuberculosis drugs merely as a determinant of non-adherence without elaborating the subsequent pathway toward the formation of resistant strains (Christy et al., 2022).

The available literature still varies in terms of population, exposure definition, and outcome. Some studies assess treatment history or resistance patterns directly, whereas other studies assess adherence, side effects, family support, or treatment outcomes. These differences make the synthesis of the three variables as a single causal model not yet justifiable. This review therefore aims to map the direction and directness of evidence regarding treatment history, medication adherence, and the side effects of anti-tuberculosis drugs, and to construct a

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

conceptual framework that is hypothetical in nature rather than a validated causal model.

RESEARCH METHOD

This study uses a structured narrative review design, not a systematic review or meta-analysis. PRISMA was used in a limited way as a transparency reporting framework. The search was conducted on Google Scholar, Portal Garuda, PubMed, and institutional repositories for Indonesian- and English-language publications from 2020 to 2026. Google Scholar and Portal Garuda were retained to capture Indonesian publications and grey literature, while PubMed was used to broaden the coverage of international biomedical publications. The Scopus, Web of Science, Embase, and Cochrane Library databases were not used. The search dates, database-specific filters, citation tracking process, and reference-list checking were not fully recorded in the source manuscript. Likewise, the deduplication log and the handling of publications with overlapping populations were not available; these limitations are stated so that the results are not positioned as a fully replicable systematic review.

Data extraction was directed at identifying author/year, setting, design, sample size, population, exposure, outcome definition, measurement method, measure of association, confounder adjustment, and methodological quality information. Evidence was separated into direct evidence when a study assessed DR-TB status or resistance patterns as an outcome, and indirect evidence when a study only assessed adherence, side effects, family support, treatment discontinuation, or therapy outcomes. No meta-analysis was performed because of heterogeneity in design, population, variable definitions, and outcomes, and because confidence intervals were not consistently available. Item-by-item appraisal using a validated instrument could not be reliably reconstructed from the available source summaries; Table 3 therefore records the quality assessment as "unclear from the available report," and this limitation was considered in the interpretation.

Table 1. Literature Search Strategy, Number of Findings, and Original Data Extraction Targets

Database	Standardized Boolean search terms	Records (initial → selected)	Data extraction target
Google Scholar	("drug-resistant tuberculosis" OR "DR-TB" OR "MDR-TB") AND ("treatment history" OR	425 → 5	Therapy history, adherence, and side

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Database	Standardized Boolean search terms	Records (initial → selected)	Data extraction target
	"adherence" OR "ATD side effects")		effects in Indonesian publications
Portal Garuda	("drug-resistant tuberculosis" OR "DR-TB") AND ("treatment history" OR "medication adherence" OR "ATD side effects")	112 → 3	Indonesian empirical data on resistance, adherence, and tolerability
PubMed (NCBI)	("Drug-Resistant Tuberculosis" OR "MDR-TB" OR "rifampicin-resistant tuberculosis") AND ("treatment history" OR "medication adherence" OR "side effects")	86 → 2	Resistance status/pattern, adherence, side effects, and measures of association
Institutional/university repositories	("DR-TB" OR "MDR-TB") AND ("adherence" OR "treatment supporter") AND ("side effects" OR "treatment history")	45 → 2	Quantitative primary data, monitoring records, and service context

Based on the available search records, four information sources produced a total of 668 initial records. The source manuscript did not retain details of the number of duplicates, the number of records screened, the number of full texts assessed, the number of full texts excluded together with the reasons, or the search dates. A complete numerical PRISMA flow therefore cannot be reconstructed without fabricating data. Twelve sources were retained in the narrative corpus, but only six studies had findings clear enough to be summarized in Table 3. These figures are consistent across the abstract, methods, results, and tables; the difference between twelve sources and six detailed studies is explained as the difference between the narrative corpus and studies with extractable data.

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Table 2. Inclusion and Exclusion Criteria Based on PEOS Parameters

Parameter (PEOS)	Inclusion criteria	Exclusion criteria
Population	TB patients undergoing treatment, including DR-TB/MDR-TB patients and, where available, a drug-sensitive TB comparison group. In studies recruiting only DR-TB patients, the outcome is interpreted as a resistance pattern or therapy outcome, not the incidence of DR-TB.	Latent TB patients, pediatric patients if they cannot be separated, or populations without relevant treatment/resistance status information.
Exposure	Prior treatment history, adherence, ATD side effects, family support, or treatment supporter measured by medical records, questionnaires, or clinical observation.	Exposures unrelated to ATD treatment or studies that discuss only genetic/pollution factors without relevant treatment variables.
Outcome	Primary outcome: DR-TB status or resistance pattern if measured directly. Secondary/contextual outcome: adherence, side effects, loss to follow-up, and therapy outcome. Secondary outcomes were not used to infer direct determinants of DR-TB.	Studies without extractable clinical or behavioral outcomes, and cost analyses without a relevant outcome.
Study design	Primary observational articles (cross-sectional, case-control, retrospective/prospective cohort) and guideline sources used for clinical context.	Literature reviews without measured data, opinions, editorials, or single case reports.

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Parameter (PEOS)	Inclusion criteria	Exclusion criteria
Year & accessibility	Publications 2020–2026 available in full text or relevant guideline sources.	Articles before 2020, abstracts only, or full texts that could not be obtained.

RESEARCH RESULTS

From the corpus of twelve sources, six studies with adequately extractable findings are summarized in Table 3. These studies did not measure the same outcome: some assessed resistance status or patterns, while others assessed adherence, side effects, family support, or treatment outcomes. The results are therefore presented as evidence mapping and are not used to conclude that all factors are direct determinants of DR-TB.

Table 3. Study Characteristics, Measurement, Effect Estimates, and Reporting Quality

Author/ year	Setting	Design	n	Population	Exposure	Outcome definition	Measurement	Effect estimate	Confounder adjustment	Methodological quality
Wahidah et al. (2024)	Indonesia	Cross-sectional	Not stated	Patients with MDR/pre-XDR or resistance pattern	First-line ATD treatment history	MDR/pre-XDR resistance status/pattern	Clinical/ medical record data as summarized	OR 2.4; CI/p not available in summary	Unclear from the available report	Unclear; item-level appraisal unavailable
Maghfiroh et al. (2025)	East Java	Retrospective descriptive	Not stated	TB-MDR patients	TB history, treatment failure, discontinuation; side effects	Resistance history/pattern and side-effect frequency	Medical records/clinical observation as summarized	OR 3.5; 5.2; 8.0; CI/p not available; neuropathy 68%	Unclear from the available report	Unclear; retrospective design and limited reporting
Christy et al. (2022)	Bengkayang, West Kalimantan	Cross-sectional	Not stated	TB patients	ATD side-effect complaints	Adherence level, not DR-TB directly	Questionnaire/observation as summarized	p<0.05; OR/CI not available	Unclear from the available report	Unclear; indirect evidence
Wiratmo et al. (2021)	Indonesia	Cross-sectional	Not stated	Pulmonary TB patients	Treatment history and side effects	Treatment adherence	Adherence instrument/clinical record as summarized	Effect size/CI not available	Unclear from the available report	Unclear; indirect evidence

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Author/ year	Setting	Design	n	Population	Exposure	Outcome definition	Measure ment	Effect estimate	Confounder adjustment	Methodol ogical quality
Fera et al. (2026)	Pegang Baru Health Center	Cross-sectional	Not stated	Adult TB patients	Knowledge of side-effect management	Treatment adherence	Questionnaire as summarized	p=0.012; OR/CI not available	Unclear from the available report	Unclear; indirect evidence
Novian et al. (2023)	Indonesia	Cross-sectional	Not stated	TB-MDR patients	Family support and treatment supporter	Medication adherence	Questionnaire as summarized	Effect size/CI not available; mediation term not used	Unclear from the available report	Unclear; indirect evidence

To prevent the combination of incomparable evidence, the synthesis is divided into four relationships. (a) The relationship between prior treatment history and DR-TB/resistance pattern is directly supported by some observational studies, including the OR reports in Wahidah et al. (2024) and Maghfiroh et al. (2025). (b) The relationship between ATD side effects and non-adherence is supported by studies assessing adherence as an outcome, such as Christy et al. (2022), Wiratmo et al. (2021), and Fera et al. (2026). (c) The relationship between non-adherence and treatment failure cannot be directly confirmed from the available study summaries because the definitions and outcomes differ. (d) The relationship between treatment failure and DR-TB is a biologically plausible mechanism and is partly reflected in treatment history, but has not been tested as a complete temporal chain in this corpus. The integrated relationship presented in Table 4 is therefore a conceptual synthesis, not a proven empirical causal model.

Treatment History

Several observational studies report a relationship between prior treatment history and resistance status or pattern. Wahidah et al. (2024) reported an OR of 2.4 for the relationship between first-line ATD treatment history and MDR/pre-XDR. Maghfiroh et al. (2025) reported an OR of 3.5 for treatment-failure history, 5.2 for treatment discontinuation/loss to follow-up, and 8.0 for recurrent TB history. These figures are odds ratios, not risk ratios or incidence ratios. Confidence intervals and individual sample sizes were not consistently available in the accessible source summaries; the precision of the estimates, the possibility of small-study effects, and cross-study comparisons must therefore be interpreted with caution.

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Medication Adherence

The literature shows variation in adherence levels among TB patients across health facilities. The findings of Wiratmo et al. (2021) and Novian et al. (2023) mainly discuss factors related to adherence, family support, or treatment supervision. These findings support the importance of support and supervision in the continuity of treatment, but do not directly prove that non-adherence causes DR-TB. Because the size, definition of non-adherence, and outcomes differ across studies, the results are not summarized as a single combined effect size.

Anti-Tuberculosis Drug Side Effects

The reported side effects were mainly somatic complaints. Maghfiroh et al. (2025) reported peripheral neuropathy at 68%, nausea and vomiting at 50%, and anorexia at 40% in the studied population. Christy et al. (2022) reported a relationship between ATD side-effect complaints and adherence level, while Fera et al. (2026) reported a relationship between knowledge of side-effect management and adherence (p=0.012). These findings suggest a possible clinical-behavioral pathway that warrants further study, but do not prove that side effects are a cause of DR-TB or a statistical mediator between exposure and outcome.

DISCUSSION

The separation between outcomes that were actually measured and theoretical interpretation is important in assessing the evidence regarding DR-TB. The relationship between treatment history and resistance status or pattern may be influenced by HIV, diabetes, nutritional status, socioeconomic conditions, smoking, alcohol consumption, prior TB episodes, treatment regimen, access to health services, social support, disease severity, and strain characteristics. Not all studies reported or adjusted for these factors, so residual confounding may explain part of the observed associations. In addition, DR-TB may be resistance acquired during treatment or resistance transmitted from a resistant strain. The OR value should therefore not be translated as absolute risk or as evidence that treatment history directly produces resistance.

The reviewed studies provide support that adherence, family support, and treatment supervision are related to the continuity of treatment or therapy outcomes. However, this evidence is not uniform and mostly does not measure DR-TB as the main outcome. Biologically, incomplete treatment can be considered a plausible mechanism, but this review cannot confirm that every episode of non-adherence ends in resistance. Terms such as "associated with treatment failure" are more appropriate to use than "causing DR-TB."

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

ATD side effects can be viewed as a possible intermediate mechanism or potential pathway linking the experience of drug toxicity with non-adherence. However, the term "mediator" is not used because the summarized studies did not report mediation analysis, path analysis, structural equation modeling, or a longitudinal design capable of testing temporality. Reverse causality needs to be considered: DR-TB patients may receive a more complex or more toxic regimen, so that side effects are actually a consequence of DR-TB treatment rather than its cause. The relationship between side effects and adherence therefore needs to be interpreted as an association that requires prospective testing and confounder control.

The mapping of the four groups of evidence is summarized in Table 4. This table is not a causal model and is not intended to state that the relationships among variables have been proven sequentially.

Table 4. Mapping of Evidence Directness and Interpretive Boundaries

Evidence category	What the included sources show	Interpretive boundary
(a) Treatment history–DR-TB/resistance pattern	Some observational studies report an association; OR 2.4–8.0 in certain sources.	OR is not a risk ratio; CIs are inconsistent; confounding and reverse causality may occur.
(b) Side effects–non-adherence	Several studies report a relationship between side effects/knowledge of side effects and adherence.	The outcome is generally adherence, not DR-TB; does not prove mediation.
(c) Non-adherence–treatment failure	Theoretically plausible, but the direct relationship is inconsistent or cannot be extracted from the source summaries.	Must not be treated as a proven empirical relationship.
(d) Treatment failure–DR-TB	Some reports of treatment-failure history/resistance pattern support a possible association.	Has not proven a complete temporal sequence; resistance may be acquired or transmitted.

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

The contribution of this study lies in the separation of four groups of evidence: treatment history–DR-TB/resistance pattern, side effects–non-adherence, non-adherence–treatment failure, and treatment failure–DR-TB. This mapping prevents evidence A (side effects–non-adherence) from being automatically combined with evidence B (treatment history–resistance) into an A–B–DR-TB claim that has not been directly tested. The relationships among variables can be used as a hypothetical framework for cohort or longitudinal research, but not as a validated causal chain.

A safer clinical implication is the need for side-effect monitoring, counseling, and adherence support from the beginning of treatment. Such interventions are worth considering to improve the continuity of therapy, but their effectiveness in preventing DR-TB needs to be tested with a design that can ensure the temporal sequence and control for confounders.

CONCLUSION

This structured narrative review shows that prior treatment history is related to resistance status or pattern in some observational studies, while adherence and side effects are more often studied as outcomes or indirect pathways. The reported ORs ranged from 2.4 to 8.0 in certain sources, but these figures are not risk ratios, confidence intervals and sample sizes were not consistently available, and the estimates were not pooled. The available evidence has not proven that side effects are a mediator or that a temporal chain of side effects → non-adherence → treatment failure → DR-TB exists. Acquired resistance and transmitted resistance must be distinguished in subsequent research. The conceptual framework presented is hypothetical and can be used to design prospective research with temporal measurement, confounder assessment, and more complete quality appraisal.

ACKNOWLEDGMENT

The authors express their appreciation and gratitude to the Public Health Study Program, Universitas Muhammadiyah Pontianak, for the academic support provided, and to the previous researchers whose scholarly work served as a valuable reference in the synthesis of this literature.

REFERENCES

Amala, A., & Cahyati, W. H. (2021). Drop out pengobatan pada tuberkulosis multidrug resistant (TB-MDR) di Kota Semarang. Quality: Jurnal Kesehatan, 15(1), 24–36. https://ejournal.poltekkesjakarta1.ac.id/index.php/adm/article/view/161

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Anisah, A., Sumekar, D. W., & Budiarti, E. (2021). Hubungan demografi dan komorbid dengan kejadian tuberkulosis resisten obat (TB RO). Jurnal Ilmiah Kesehatan Sandi Husada, 10(2), 568–574. https://doi.org/10.35816/jiskh.v10i2.655

Christy, B. A., Susanti, R., & Nurmainah, N. (2022). Hubungan tingkat kepatuhan minum obat pasien tuberkulosis terhadap efek samping obat anti tuberkulosis (OAT). Jurnal Syifa Sciences and Clinical Research, 4(1), 484–493. https://doi.org/10.37311/jsscr.v4i2.14830

Fera Desi Nila Sari, Efmisa, A. K., & Armal, K. (2026). Hubungan tingkat pengetahuan dengan kepatuhan pengobatan dalam menghadapi efek samping obat TB dewasa di Puskesmas Pegang Baru. Al-Syifa: Journal of Medical and Public Health Sciences, 1(1), 12–20. https://doi.org/10.1111/alsyifa.v1i1.140

Fitriangga, A., et al. (2025). Edukasi kader dan skrining risiko putus obat TB di wilayah pesisir Pontianak. Jurnal SOLMA, 14(3), 3862–3871. https://garuda.kemdiktisaintek.go.id/documents/detail/5797890

Kementerian Kesehatan RI. (2019). Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/MENKES/755/2019 tentang Pedoman Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis. Jakarta: Kementerian Kesehatan RI.

Kementerian Kesehatan RI. (2020). Temukan TB obati sampai sembuh: Penatalaksanaan tuberkulosis resisten obat di Indonesia. Jakarta: Kementerian Kesehatan RI.

Maghfiroh, I. L., Pradita, P. E., & Samantha, H. (2025). Efek samping pemberian obat anti tuberkulosis (OAT) pada pasien tuberkulosis multiple drug resistance (TB MDR). Journal of Language and Health, 6(1), 89–97. https://doi.org/10.37287/jlh.v6i1.5998

Manggasa, D. D., & Suharto, D. N. (2022). Riwayat pengobatan dan komorbid diabetes mellitus berhubungan dengan kejadian tuberkulosis resisten obat. Poltekita: Jurnal Ilmu Kesehatan, 15(4), 403–408. https://doi.org/10.33860/jik.v15i4.659

Novian, L., et al. (2023). Dukungan keluarga terhadap kepatuhan minum obat pada penderita tuberculosis dengan multidrug resistant (TB-MDR). Journal of Telenursing (JOTING), 5(2), 1650–1658. https://doi.org/10.31539/joting.v5i2.6530

Salsabila, L. Z., Susanti, R., & Bhakti, W. K. (2022). Analisis faktor tingkat kepatuhan minum obat anti tuberkulosis pada pasien TB paru rawat jalan di Puskesmas Perumnas 1 Kota Pontianak tahun 2021. Jurnal Mahasiswa Farmasi Fakultas Kedokteran UNTAN, 6(1), 1–8.

Wahidah, N., et al. (2024). Determinan pola resistensi pasien multi-drug resistant tuberculosis (MDR-TB). Indonesian Journal of Pharmaceutical Education, 4(1), 56–67. https://doi.org/10.37311/ijpe.v4i1.24636

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License

Wiratmo, P. A., Setyaningsih, W., & Fitriani. (2021). Riwayat pengobatan, efek samping obat dan penyakit penyerta pasien tuberkulosis paru terhadap tingkat kepatuhan berobat. CoMPHI Journal: Community Medicine and Public Health of Indonesia Journal, 2(1), 30–36. https://doi.org/10.37148/comphijournal.v2i1.46

World Health Organization. (2025). Global tuberculosis report 2025. Geneva: World Health Organization.

Copyright at authors some right reserved this work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License