Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: https://www.ijmmtd.org/

Case Series

Exploring adverse drug reactions in first-line antitubercular treatment: A case series

Pedada Mounika[1], Elen Ann Abraham[1]*, Ghanshyam Verma[1], Akhil Anand[1], Keerthana Priya[1]

[1]Dept. of Respiratory Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India

Abstract

Managing adverse drug reactions (ADRs) remains a significant hurdle despite the high efficacy of standard anti-tuberculosis treatments. The majority of ADRs were classified as clinical (53%), predominantly occurring early in treatment (82.5%) and characterized as mild to moderate (88.7%), mainly falling under "metabolic and nutritional disorders." Interestingly, while there were no significant differences in ADR types, severity, or causality between early and late occurrences, the early group showed a higher incidence of metabolic and gastrointestinal disorders, whereas skin-related issues were more prevalent in the late stage of treatment. These findings underscore the frequent occurrence of ADRs throughout TB treatment, emphasizing the importance of vigilant monitoring and timely intervention to enhance patient safety and treatment adherence.

Keywords: Adverse drug reactions, Anti-TB Treatment, Directly observed pulmonary tuberculosis, Treatment short-course, Tuberculosis.

Received: 21-04-2025; **Accepted:** 19-05-2025; **Available Online**: 28-05-2025

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains a formidable global health challenge, with staggering implications outlined by the World Health Organization (WHO) in their 2019 report. An estimated 10 million people worldwide were infected, resulting in 1.4 million deaths attributed to TB. The urgency of early detection and timely treatment is underscored by the effectiveness of standard anti-TB treatment (ATT) tempered by the substantial challenge of managing drug toxicity, manifesting primarily as adverse drug reactions (ADRs).[1-4] These ADRs not only disrupt treatment continuity but also diminish cure rates and heighten the risk of multidrug-resistant TB (MDR-TB). Varied in severity and potentially occurring at any stage of treatment, ADRs pose significant threats to patient health, necessitating vigilant monitoring and intervention strategies to mitigate the impact.[5-8]

Pharmacovigilance, as defined by WHO, assumes a pivotal role in this landscape, encompassing the detection, assessment, understanding, and prevention of ADRs and other drug-related issues.[9,10] This scientific discipline is essential in clinical settings, where the limitations of initial trials often obscure broader implications seen only after medications are disseminated widely among diverse patient populations.[11-14] Monitoring medications throughout their lifecycle becomes imperative to preemptively address ADRs that could otherwise escalate to severe outcomes, including increased hospitalizations and mortality.[15-18]

In the context of public health initiatives like TB management, pharmacovigilance assumes heightened importance given the protracted and multi-drug nature of treatment regimens. Despite the complexities, ensuring patient compliance remains paramount to averting treatment failures and resisting the emergence of drug-resistant strains.[19-21] Effective management of ADRs, such as those exacerbated by medications like rifampicin and isoniazid, underscores the need for strategic interventions to sustain treatment efficacy and reduce the burdensome toll on healthcare systems worldwide.[22]

*Corresponding author: Elen Ann Abraham
Email: drelenann153@gmail.com

http://doi.org/10.18231/j.ijmmtd.2025.039

TB, predominantly affecting the lungs and compounded by its airborne transmission, disproportionately impacts vulnerable populations, including those with HIV/AIDS, exacerbating the global health challenge. The WHO-endorsed directly observed treatment short-course (DOTS) therapy, while pivotal in TB management, presents its own set of challenges due to associated ADRs.[23-25] Addressing these complexities through comprehensive pharmacovigilance efforts not only enhances patient safety and treatment outcomes but also represents a crucial step towards mitigating the global TB burden effectively.[25-30]

2. Case Report

2.1. Case 1

A 56 year male patient, was diagnosed with active tuberculosis and started on standard ATT regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol. Due to the development of drug resistance, levofloxacin was introduced as part of the treatment regimen. Approximately 1 week after initiation of levofloxacin, the patient experienced a generalized tonic- clonic seizure. There was no prior history of seizures or epilepsy. The patient was promptly brought to the Emergency Department of Sree Balaji Medical College and Hospital, Chennai where antiepileptic treatment was initiated and the patient was stabilized. Blood tests including complete blood count, electrolytes, and renal function were within normal limits. Chest X-ray showed patchy areas of consolidation in the right upper, middle and lower lobe.(**Figure 1**)

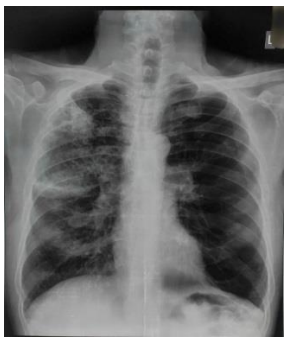

Figure 1: Patchy areas of consolidation in right upper, middle and lower lobes

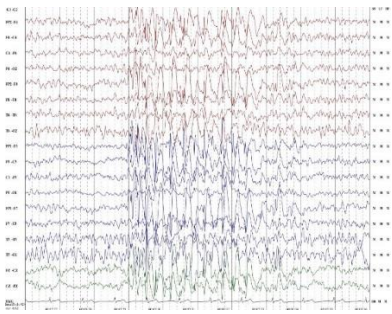

Figure 2: EEG showing epileptiform activity

Electroencephalogram (EEG) Showed generalized epileptiform activity consistent with seizure.(**Figure 2**)

2.2. Case 2

A 45 year male, was diagnosed with pulmonary tuberculosis and initiated on standard ATT regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol. During the course of ATT, the patient developed skin lesions characterized by erythematous rash on dorsum, upper and lower extremities. The lesions were associated with symptoms such as itching or pain. The onset of skin lesions occurred approximately 8 weeks after starting ATT.(**Figure 3**,**Figure 4**,**Figure 5**)

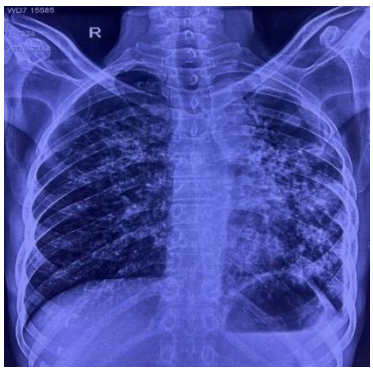

Figure 3: Bilateral patchy infiltrates are more in left lung field.

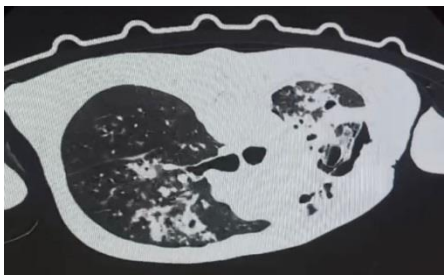

Figure 4: CT Chest showed multiple small patchy areas of consolidation and cavitations in bilateral upper and left lower lobe. Multiple small patchy consolidation with centrilobular nodules in bilateral lung segments. Reduced lung volume on left side and mediastinal shift to left with left costal and mediastinal pleural thickening and mediastinal lymphadenopathy

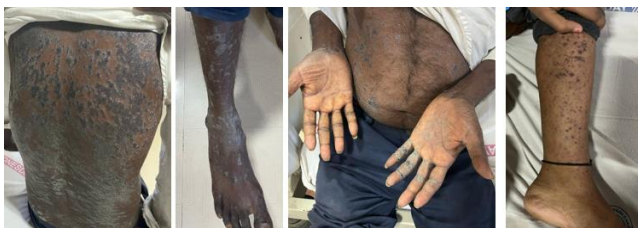

Figure 5: Erythematous rash on Dorsum, upper and lower extremities

2.3. Case 3

A 26 year old female, was diagnosed with pulmonary tuberculosis and started on standard ATT regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol. Chest x-ray showed patchy consolidation in the bilateral lower lung fields (**Figure 6**). During routine monitoring, approximately [duration after starting ATT], the patient's liver function tests showed elevated liver enzymes beyond normal limits. The patient did not report any symptoms suggestive of liver dysfunction such as jaundice or abdominal pain. Liver function tests revealed elevated levels of alanine aminotransferase (ALT)-53 IU/L, aspartate aminotransferase (AST)-140 IU/L.

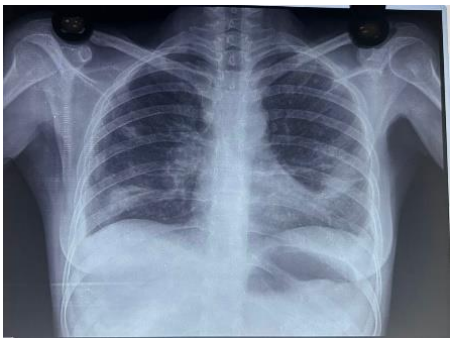

Figure 6: Patchy consolidation noted in bilateral lower lung fields

Figure 7: Painless erythematous rash on face and neck

The patient developed skin lesions characterized by erythematous rash which are painless on face and neck.(**Figure 7**) The onset of skin lesions occurred approximately 4 weeks after starting ATT. Concerned about ATT-induced hepatotoxicity, the patient's ATT regimen was reassessed. Rifampicin was temporarily discontinued, and the patient was closely monitored with liver function tests and clinical assessments.

2.4. Case 4

A 23 year male patient, exhibited signs of acute illness with a high-grade fever and generalized weakness. Chest X-ray and subsequent CT scan demonstrated diffuse micronodular opacities throughout both lung fields, characteristic of miliary tuberculosis. The patient was promptly started on a standard regimen of anti-tuberculosis treatment (ATT) comprising isoniazid, rifampicin, pyrazinamide, and ethambutol.(**Figure 8**)

The patient exhibited acute-onset psychosis characterized by symptoms like hallucinations and delusions. This manifested as a sudden change in behavior and impaired functional capacity within the operational setting. Given the urgency of the situation and INH was promptly discontinued upon suspicion of drug-induced psychosis. Antipsychotic medication was initiated, and alternative anti-tuberculosis medications were adjusted without INH.

Figure 8: Bilateral scattered Miliary shadows

3. Discussion

Ensuring effective treatment adherence is crucial in achieving successful outcomes in tuberculosis (TB), with adherence rates exceeding 90% essential to prevent drug-resistant strains and reduce disease transmission, ultimately lowering mortality and morbidity rates.[31-33] Our study delved comprehensively into adverse drug reactions (ADRs) among patients with pre-extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR) TB, providing vital insights into treatment management.[34-35]

Various drug therapies are administered for tuberculosis (TB), particularly for new TB patients who are sensitive to first-line drugs.[36] These patients receive a treatment regimen consisting of a combination of four drugs to ensure effective management. Monitoring for adverse drug reactions (ADRs) is crucial during treatment to maintain compliance until the completion of Anti-Tuberculosis Treatment (ATT).[37] For TB patients with drug-resistant forms such as multidrug-resistant or extensively drug-resistant TB, treatment may involve a higher number of drugs, necessitating vigilant identification and management of associated ADRs. Proper treatment adjustments are essential if any ADR occurs. TB patients co-infected with HIV require careful management due to potential overlapping medication effects between TB and HIV treatments, including antiretroviral therapy.[37] Monitoring this population closely ensures efficient treatment management. Special medical conditions in TB patients, such as diabetes mellitus, liver disease, renal disorders, seizure disorders, or psychosis, demand cautious

treatment approaches.[38] Progress should be closely observed, and all encountered ADRs meticulously monitored. Additionally, with the introduction of new drugs like Bedaquiline (BDQ), Delamanid (DLM), and Pretomanid in TB programs, prompt detection and management of associated ADRs are essential for effective TB treatment.[38]

The Anti-Tuberculosis Treatment (ATT) regimen, comprising a combination of multiple medications over an extended period, is known to increase the likelihood of adverse drug reactions (ADRs).[35] Gastrointestinal symptoms such as nausea and vomiting are among the most frequently encountered ADRs, typically managed symptomatically without necessitating dosage adjustments. Hepatotoxicity is another concern, with varying frequencies observed globally, including a notably higher incidence among the Indian sub-population compared to Western populations.[36,37] Isoniazid, while generally well-tolerated at recommended doses, can occasionally lead to systemic or cutaneous hypersensitivity reactions early in treatment, necessitating caution. Supplementation with pyridoxine helps mitigate the risk of peripheral neuropathy in vulnerable patients, although some may develop more severe neurological disturbances later on, potentially requiring discontinuation of the drug. Asymptomatic elevations in liver enzymes are common at the onset of treatment but typically resolve spontaneously without clinical significance. Less common but serious reactions such as symptomatic hepatitis may require immediate cessation of treatment, while rare ADRs include lupus-like syndrome, pellagra, anemia, and arthralgias.[38]

Pyrazinamide, another first-line drug, is frequently associated with cutaneous ADRs and gastrointestinal intolerance, though hypersensitivity reactions are rare. Moderate increases in liver enzymes are common early in treatment, and severe hepatotoxicity is a rare but serious complication. Hyperuricemia may occur, potentially leading to gout, which can be managed with allopurinol. Arthralgia, particularly in the shoulders, is another reported ADR that can be alleviated with simple analgesics. Intermittent administration schedules can help mitigate these effects.[37] Streptomycin, although no longer recommended by WHO, may still be used in some contexts where alternatives like kanamycin or amikacin are employed, all of which carry risks of painful injections, rash, and ototoxicity, with vestibular impairment being uncommon but possible. Ethambutol usage can lead to optic neuritis affecting visual acuity and color vision, which can be reversible if detected early. Peripheral neuropathy and other rare adverse events such as cutaneous reactions and hepatitis have also been reported.[39] Monitoring and managing these ADRs are critical to ensuring effective treatment adherence. While less severe reactions may not require discontinuation of drugs, serious ADRs often necessitate adjustments to treatment regimens for patient safety.[40]

Cardiovascular implications, particularly QTCF prolongation associated with BDQ and DLM, prompted regulatory warnings about risks like sudden death. Gastrointestinal disturbances were prominent early in treatment, necessitating swift interventions. Arthralgia and psychosis, linked respectively to pyrazinamide and cyclosporine, were notable ADRs. Hepatotoxicity was recurrent, exacerbated by medications such as pyrazinamide and BDQ, necessitating stringent liver function monitoring. Peripheral neuropathy, albeit rare, posed challenges, particularly with ethionamide and kanamycin.[41-45]

Uncommon ADRs included hypothyroidism, tremors, and vestibular disorders, each requiring tailored interventions amidst treatment complexities.[45]

4. Conclusion

The challenge of adverse drug reactions (ADRs) remains a significant global health concern, consistently ranking among the top causes of mortality worldwide. Early detection and prevention of ADRs during tuberculosis (TB) treatment are crucial to promoting the rational use of medications and mitigating the burden of antimicrobial resistance. Strengthened adherence among targeted populations facilitates effective monitoring and transparent communication about treatment risks and benefits, thereby improving decision-making in medicine procurement. Monitoring the safety of medications is fundamental to the integrity of any resilient health system. Therefore, comprehensive reporting of ADRs is essential, as it reinforces evidence-based practices, optimizes therapeutic outcomes, and minimizes associated risks.

In conclusion, our study provides crucial insights into ADRs among patients with pre-XDR, underscoring the imperative for enhanced pharmacovigilance in treatment protocols. Moving forward, the implementation of robust monitoring frameworks and the advancement of therapeutic strategies are indispensable for maximizing patient safety and improving treatment outcomes in the effective management.

5. Conflict of Interest

The authors hereby declare that there is no conflict of interest in this study.

6. Sources of Funding

The Authors received no external funding and covered all costs personally.

Acknowledgement

We would like to express our sincere gratitude to all the patients and their families for their participation and consent, which made this case series possible. We also thank the medical and support staff involved in the care of these patients for their invaluable assistance and collaboration.

Special thanks to Dr.Elen Ann Abraham, Associate Professor, for their critical insights and guidance throughout the preparation of this manuscript. We acknowledge Department of Respiratory Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu for providing the resources necessary to carry out this work.

References

1. Initiative (World Health Organization), Eds., Treatment of tuberculosis: guidelines, 4th ed. Geneva: World Health Organization, 2010.
2. "WHO_HTM_TB_2014.23_eng.pdf." Accessed: Mar. 17, 2021. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/137334/WHO_HTM_TB_2014.23_eng.pdf;jsessionid=3F28C9E7FB3CC604788D92E5CEB971F8?sequence=1.
3. World Health Organization, WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. https://www.who.int/publications/i/item/9789241550529
4. Anand AC, Seth AK, Paul M, Puri P. Risk Factors of Hepatotoxicity during Anti-tuberculosis Treatment. *Med J Armed Forces India*. 2011;62(1):45–9.
5. Parthasarathy R, Sarma GR, Janardhanam B, Ramachandran P, Santha T, Sivasubramanian S, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1986;67(2):99-108.
6. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today*. 2015;105(2):140–56.
7. World Health Organization, Handbook of resolutions and decisions of the World Health Assembly and the Executive Board. World Health Organization, 1973. https://iris.who.int/handle/10665/79012
8. Pharmacovigilance - an overview | ScienceDirect Topics. (Accessed Feb. 24, 2021). https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pharmacovigilance
9. Berlin JA, Glasser SC, Ellenberg SS. Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3. *Am J Public Health*. 2008;98(8):1366–71.
10. Raj N, Fernandes S, Charyulu NR, Dubey A, Ravi GS, Srinivas H. Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. *Ther Adv Drug Saf*. 2019;10:10.1177/2042098619865413.
11. Thomas RI, Cameron DJ, Fahs MC. A Prospective Study of Delirium and Prolonged Hospital Stay: Exploratory Study. *Arch Gen Psychiatry*. 1988;45(10):937–40.
12. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis." Accessed: Mar. 17, 2021. [Online]. Available: https://www.who.int/docs/default-source/documents/tuberculosis/a-practical-handbook-on-the-pharmacovigilance-of-medicines-used-in-the-treatment-of-tuberculosis.pdf?sfvrsn=6e5fc0cf_5.
13. Imam F, Sharma M, Khayyam KU, Al-Harbi NO, Rashid MK, Ali MD, et al., "Adverse drug reaction prevalence and mechanisms of action of first-line anti-tubercular drugs. *Saudi Pharm J*. 2020;28(3):316–24.
14. Agrawal V, Shrivastava TP, Adusumilli PK, Vivekanandan K, Thota P, Bhushan S. Pivotal role of Pharmacovigilance Programme of India in containment of antimicrobial resistance in India. *Perspect Clin Res*. 2019;10(3):140–4.
15. Hoffmann C. Pulmonary tuberculosis in adults in Tuberculosis, Elsevier, 2009:332–41.
16. Todorova TT, Tsankova G, Lodozova N, Kostadinova T. Tuberculosis and HIV — Doubling the Fatality [Internet]. Immunopathology and Immunomodulation. InTech; 2015. Available from: http://dx.doi.org/10.5772/61138.
17. Bruchfeld J, Correia-Neves M, Källenius G. Tuberculosis and HIV Coinfection. *Cold Spring Harb Perspect Med*. 2015;5(7):a017871.
18. Global tuberculosis programme. 2013. https://www.who.int/publications-detail-redirect/9789241564656.
19. Tuberculosis: multidrug-resistant tuberculosis (MDR-TB). 2018. https://www.who.int/newsroom/questions-and-answers/item/tuberculosis-multidrug-resistant-tuberculosis-(mdr-tb).
20. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis treatment non-adherence and lost to follow up among TB patients with or without HIV in developing countries: A systematic review. *Iran J Public Health*. 2015;44(1):1–11.
21. Collins D, Njuguna C. The Economic Cost of Non-adherence to TB Medicines Resulting from Stock-Outs and Loss to Follow-up in Kenya. Management Sciences for Health, Arlington, VA; 2016. https://msh.org/wp-content/uploads/2017/05/17-029_siaps_kenya_report.pdf
22. Haagsma AC, Podasca I, Koul A, Andries K, Guillemont J, Lill H, et al. Probing the interaction of the diarylquinoline TMC207 with its target mycobacterial ATP synthase. *PLoS One*. 2011;6:10.1371/journal.pone.0023575.
23. India's pharmacovigilance regime. (2018). https://www.mondaq.com/india/healthcare/751258/india39s-pharmacovigilance-regimen https://www.mondaq.com/india/healthcare/751258/india39spharmacovigilance-regimen.
24. TB/HIV: A clinical manual. 2004. https://iris.who.int/bitstream/handle/10665/42830/9241546344.pdf?sequence=1.
25. Global tuberculosis report 2015. 2015. https://apps.who.int/iris/handle/10665/191102.
26. Young F, Critchley JA, Johnstone LK, Unwin NC. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. *Global Health*. 2009;5:10.1186/1744-8603-5-9
27. Yone EW, Kengne AP, Kuaban C. Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study. *BMJ Open*. 2011;1:10.1136/bmjopen-2011-000289
28. Equatorial Guinea DHS, 2011 - final report. [Report in Spanish]. 2011. https://dhsprogram.com/publications/publication-fr271-dhs-final-reports.cfm.
29. Gube AA, Debalkie M, Seid K, Kiberalem B, Asfaw M, Abubeker Z, et al. Assessment of anti-TB drug nonadherence and associated factors among TB patients attending TB clinics in Arba Minch governmental health institutions, *Southern Ethiopia. Tuberc Res Treat*. 2007;54:66–70.
30. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371(8):723–32.
31. Kalbhairav MS, Shraddha MP, Tushar RB. Adverse reactions to first-line anti-tuberculous agents in hospitalised patients: pattern, causality, severity and risk factors. *Indian J Medical Spec*. 2013;4:16–21.
32. Tak DK, Acharya LD, Gowrinath K, Padma GM, Subish P. Safety evaluation of antitubercular therapy under Revised National Tuberculosis Control Programme in India. *J Clin Diagn Res*. 2009;3:1395–401.
33. Arora VK, Tumbanatham A. Severe arthropathy with ofloxacin in two cases of MDR tuberculosis. *Int J Tuberc Lung Dis*. 1998;2(11):941–3.
34. Vega P, Sweetland A, Acha J, Castillo H, Guerra D, Smith Fawzi MC, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2004;8(6):749–59.
35. Devarbhavi H. Antituberculous drug-induced liver injury: current perspective. *Trop Gastroenterol*. 2011;32(3):167–74.

36. Ormerod LP, Horsfield N: Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuber Lung Dis*. 1996;77(1):37–42.
37. World Health Organization. Global Tuberculosis Report 2020. Geneva, 2020. https://www.who.int/publications/i/item/9789240013131
38. World Health Organization. Drugs and Therapeutics Comittee Training Course Agency for International Development by the Rational Pharmaceutical Managenment. Geneva, 2007.
39. Horsburgh CR Jr, Barry CE 3rd, Lange C. Treatment of Tuberculosis. *N Engl J Med*. 2015;373(22):2149–60.
40. World Health Organization, The End TB Strategy. https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/the-end-tb-strategy
41. Aouam K, Chaabane A, Loussaief C, Ben Romdhane F, Boughattas NA, Chakroun M. Adverse Effects of Antitubercular Drugs: Epidemiology, Mechanisms, and Patient Management. *Med Mal Infect*. 2007;37(5):253–61.
42. Aziz K, Shahbaz A, Umair M, Sharifzadeh M, Sachmechi I. Hyperprolactinemia With Galactorrhea Due to Subclinical Hypothyroidism: A Case Report and Review of Literature. *Cureus*. 2018.10:e2723.
43. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol Optic Neuropathy. *Curr Opin Ophthalmol*. 2017;28(6):545–51.
44. Srikanth BA, Babu SC, Yadav HN, Jain SK. Incidence of Adverse Drug Reactions in Human Immune Deficiency Virus-Positive Patients Using Highly Active Antiretroviral Therapy. *J Adv Pharm Technol Res*. 2012;3(1):62–7.
45. Michael OS, Sogaolu OM, Fehintola FA, Ige OM, Falade CO. Adverse Events to First Line Anti-Tuberculosis Drugs in Patients Co-Infected With Hiv and Tuberculosis. *Ann Ib Postgrad Med*. 2016;14(1):21–9.

Cite this article: Mounika P, Abraham EA, Verma G, Anand A, Priya K. Exploring adverse drug reactions in first-line antitubercular treatment: A case series. *IP Int J Med Microbiol Trop Dis.* 2025;11(2):242-247.