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SAFETY OF ANTITUBERCULOSIS AGENTS USED FOR MULTIDRUG-RESISTANT TUBERCULOSIS: A REVIEW OF EVIDENCE FROM CAMEROON

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) — defined by resistance to isoniazid and rifampicin — remains a severe public health threat in sub-Saharan Africa, where treatment requires prolonged, multi-drug regimens with substantial toxicity. This review synthesizes a thesis comprising three linked retrospective/prospective cohort studies conducted at the Jamot Hospital of Yaoundé (JHY), Cameroon's principal MDR-TB referral center, examining the safety and drug-utilization profile of successive World Health Organization (WHO)-recommended regimens between 2017 and 2023. The first study (2017–2019, N = 107) found that 89.7% of patients experienced at least one adverse drug reaction (ADR), with aminoglycoside-related ototoxicity affecting nearly two-thirds of patients and driving most dose reductions. The second study, drawn from the same cohort, found 91.5% compliance with WHO prescribing guidelines but only 51.4% overall treatment persistence, with the sharpest attrition occurring in the ambulatory continuation phase. The third study (2021–2023, N = 53) evaluated the regimen after aminoglycosides were replaced with bedaquiline: ototoxicity was eliminated, and persistence to initial therapy was nearly complete, but new safety signals emerged, including arthralgia, hepatotoxicity, peripheral neuropathy, QT-interval prolongation, and two sudden deaths. Taken together, the findings show that MDR-TB treatment in Cameroon remains a moving target for pharmacovigilance: each guideline revision that resolves one toxicity profile introduces another, underscoring the need for a functioning national active drug-safety monitoring (aDSM) system, particularly for

cardiovascular risk associated with bedaquiline-containing regimens.

1. INTRODUCTION

Tuberculosis (TB) has been designated a global public health emergency by the World Health Organization since 1994, and multidrug-resistant tuberculosis (MDR-TB) — TB resistant to the two most effective first-line drugs, isoniazid and rifampicin — represents one of its most difficult clinical manifestations. Untreated MDR-TB carries a fatality rate of 20–70%, and even with treatment, global cure rates hover around 57%. Cameroon is among the higher-burden countries for TB-HIV co-infection in Africa, with a national TB mortality rate of approximately 2.9%, and its National Tuberculosis Program (NTP) has adopted successive WHO-recommended regimens for MDR-TB over the past decade.

The thesis under review addresses a central but underexplored dimension of MDR-TB care: drug safety. While WHO guideline updates are typically framed around efficacy and treatment duration, each new regimen also introduces a distinct toxicity profile, and the practical consequences of these trade-offs — for patient persistence, adverse event burden, and pharmacovigilance capacity

— are rarely documented in low-resource settings. This review summarizes three interconnected studies conducted at the Jamot Hospital of Yaoundé that trace the safety and utilization profile of MDR-TB treatment in Cameroon across two successive WHO guideline eras, and it situates these findings within the broader literature on MDR-TB pharmacovigilance.

2. Background: Evolution of WHO MDR-TB Treatment Guidelines

Historically, MDR-TB was managed with individualized regimens lasting 18–20 months, guided by drug-susceptibility testing. In May 2016, WHO introduced a standardized "shorter treatment regimen" (STR) of 9–12 months for patients without fluoroquinolone or second-line injectable resistance. The STR's intensive phase (4–6 months) combined seven drugs — including an injectable aminoglycoside (kanamycin or amikacin) — followed by a 5-month continuation phase of four oral drugs.

In June 2020, WHO revised this guidance to recommend an all-oral 9–11 month regimen in which bedaquiline replaced the injectable aminoglycoside, primarily to address aminoglycoside-associated ototoxicity, alongside a conditional new BPaL regimen (bedaquiline, pretomanid, linezolid) for patients with additional fluoroquinolone resistance. By 2022, WHO guidance had evolved further to endorse a 6-month BPaLM regimen (adding

moxifloxacin), reporting success rates as high as 89% compared with 52% for earlier shorter regimens, alongside a continued 9-month all-oral option for patients ineligible for BPaLM. Cameroon's NTP adopted the bedaquiline-based all-oral regimen in November 2021.

Pharmacovigilance — the science of detecting, assessing, and preventing adverse drug reactions

— is essential to managing the toxicity trade-offs inherent in each guideline revision. Approaches range from passive spontaneous reporting (simple but prone to severe underreporting, capturing under 1% of true ADRs) to active surveillance methods such as cohort event monitoring, sentinel-site surveillance, and longitudinal electronic records. In Cameroon, the NTP relies almost exclusively on passive spontaneous reporting through a single pharmacist serving as the pharmacovigilance focal point; as of September 2023, VigiBase had recorded only three anti-tuberculosis-related adverse event reports for the entire country, a figure that stands in stark contrast to the adverse event burden documented in the studies reviewed here.

3. Study 1: Safety of Antituberculosis Agents at Jamot Hospital (2017–2019)

3.1 Methods

This retrospective cohort study followed 107 adult MDR-TB patients treated at JHY between January 2017 and December 2019 under the WHO 2016 shorter treatment regimen. Adverse drug reactions were extracted from medical records and graded 1–5 using a scale equivalent to the Common Terminology Criteria for Adverse Events, with descriptive statistics computed in R.

3.2 Key Findings

Nearly 90% of patients (96/107) experienced at least one ADR, generating 448 total ADR events (4.5 per patient), though 84.1% of these were mild or moderate. Hearing impairment was the dominant safety signal, affecting 65.4% of patients — far exceeding the 10–50% incidence WHO had anticipated — and accounting for 96.7% of dose reductions and half of all drug substitutions. Gastrointestinal effects (vomiting, nausea) were the next most common. Six patients (5.6%) experienced severe (Grade ≥3) events, including three deaths (two HIV-positive patients within the first month, one at seven months), two cases of acute kidney injury linked to HIV nephropathy, and one myocardial infarction. HIV-positive patients experienced hearing loss at a substantially higher rate (71.7%) than HIV-negative patients, and audiogram monitoring — conducted only at months two and four — was not systematically followed by clinical intervention.

4. Study 2: Drug Utilization and Treatment Persistence

4.1 Methods

Using the same 2017–2019 cohort, this study assessed adherence to WHO 2016 dosing recommendations and patient persistence — defined separately for the overall program, the intensive phase, the continuation phase, and persistence to the originally prescribed therapy without modification.

4.2 Key Findings

Prescribing compliance with WHO guidelines was high: 91.5% of patients (98/107) began treatment on a guideline-concordant regimen, with the few non-conformities concentrated among female patients and those weighing 30–39 kg. However, only 51.4% of patients ultimately completed the full MDR-TB program. Persistence was markedly phase-dependent: 90.6% of patients completed the hospitalized intensive phase, but only 61.8% of those who began the ambulatory continuation phase persisted to its end. Most attrition, in both phases, occurred within the first 30 days. Of the 107 patients, 28% (30 patients) required a drug or dose adjustment — 26 of 31 dose reductions were aminoglycoside-related, driven by hearing loss — and persistence to the original, unmodified regimen was 72.1% among those who completed the intensive phase.

5. Study 3: Safety and Persistence After the Introduction of Bedaquiline (2021–2023)

5.1 Methods

This preliminary prospective cohort study followed 53 MDR-TB patients through the intensive phase (4–6 months) of the WHO 2020 all-oral, bedaquiline-based regimen at JHY between November 2021 and July 2023, evaluating prescribing conformity, persistence, and ADR occurrence using the same grading approach as Study 1.

5.2 Key Findings

Ototoxicity was completely absent in this cohort — a marked contrast to the earlier aminoglycoside-based regimen. Persistence to initial therapy was correspondingly excellent: 96.2% of patients persisted through the intensive phase, and none required a dose change or drug switch due to ADRs. However, 71.7% of patients still experienced at least one ADR, predominantly mild (Grade 1: 88.6%), including vomiting (26.4%), arthralgia (26.4%), peripheral neuropathy (9.4%), and elevated liver enzymes (7.5%). More concerning, the cohort recorded two sudden deaths (at 16 and 45 days of treatment, in an HIV-positive patient and a hepatitis-C-coinfected patient respectively) and two cases of cardiac palpitations, alongside systematic dosing non-conformities for moxifloxacin (400 mg given regardless of

weight class rather than the recommended 600–800 mg) and clofazimine (100 mg given to low-weight patients rather than the recommended 50 mg).

6. Discussion: Synthesis and Comparison with the Broader Literature

Read together, the three studies trace a coherent narrative of "shifting toxicity" across guideline eras. The 89% overall ADR incidence documented in Study 1 exceeds figures reported in comparable cohorts in Russia (73%) and India (58%), and the 65% ototoxicity rate substantially exceeds WHO's own projected range of 10–50%. This is broadly consistent with other African and low-resource-setting studies — for example, work in Zambia and South Africa has similarly identified aminoglycosides as the dominant driver of irreversible hearing loss in MDR-TB cohorts, and Hong et al. specifically link HIV co-infection to elevated aminoglycoside-induced hearing loss risk, a pattern mirrored in this Cameroonian cohort.

The persistence findings in Study 2 echo a recurring theme in the MDR-TB literature: attrition concentrated in the ambulatory continuation phase, when patients lose the structure and monitoring of hospitalization. This aligns with prior observations (e.g., Mason et al. in Papua New Guinea) that unsupervised, at-home phases of MDR-TB treatment are disproportionately vulnerable to non-persistence, with consequences for both individual outcomes and the population-level risk of extensively drug-resistant TB (XDR-TB).

Study 3's findings are consistent with the rationale behind WHO's 2020 guideline revision: replacing aminoglycosides with bedaquiline did eliminate ototoxicity and dramatically improved persistence to initial therapy, corroborating the guideline change at the country level. However, the emergence of cardiovascular signals — palpitations, and two deaths that could not be conclusively linked to or excluded from drug causality — echoes a well-documented concern in the pharmacology literature regarding QT-interval prolongation from bedaquiline, particularly when co-administered with clofazimine and moxifloxacin, both of which independently carry cardiac risk. This triple combination, used concurrently during the intensive phase in Cameroon's current regimen, represents a specific and identifiable monitoring priority that the reviewed thesis explicitly flags.

A further consistent thread across all three studies is the gap between the volume of clinically documented ADRs and what reaches Cameroon's national pharmacovigilance system: only three anti-tuberculosis ADRs nationally were logged in VigiBase as of September 2023, despite hundreds of ADR events documented in the JHY medical records alone reviewed in this thesis. This mirrors a broader pattern documented by Ampadu et al. of substantial underreporting to global pharmacovigilance databases from African countries relative to the

rest of the world.

7. Methodological Strengths and Limitations

7.1 Strengths

- A coherent three-study design that tracks the same referral center (responsible for roughly two-thirds of Cameroon's MDR-TB caseload) across two successive guideline eras, allowing direct before/after comparison of the aminoglycoside-based and bedaquiline-based regimens.
- Use of a standardized, internationally recognized ADR severity grading scale (equivalent to CTCAE Grades 1–5), enabling comparison with international cohorts.
- Explicit tracking of persistence at multiple levels — overall program, phase-specific, and persistence to the original unmodified regimen — which reveals where in the treatment pathway attrition actually occurs, rather than relying on a single aggregate completion rate.
- Direct clinical relevance: findings map onto specific, actionable monitoring priorities (audiometry timing, ECG monitoring, weight-based dosing accuracy).

7.2 Limitations

- All three studies are single-center (Jamot Hospital of Yaoundé), which, while representative of a large share of Cameroon's MDR-TB caseload, limits generalizability to smaller or rural treatment centers with different staffing and monitoring capacity.
- Studies 1 and 2 are retrospective and rely on physician-documented ADRs in medical records; this likely underestimates true ADR incidence, particularly for symptoms patients may not have reported or that were not systematically probed (a limitation the original authors acknowledge).
- Sample sizes are modest (107 and 53 patients respectively), limiting statistical power to detect associations between patient characteristics and specific rare adverse events, such as the sudden deaths and cardiac events noted in Study 3.
- Study 3 is described as preliminary/an article in preparation, with a shorter follow-up window (intensive phase only) than the full treatment course, so conclusions about continuation-phase safety under the bedaquiline-based regimen remain incomplete.
- Reviewers should note an inconsistency in the source document's front matter: the cover page and declaration attribute the thesis to two different names and describe it as a Master's thesis on "Prevalence of MDR-TB in Bathinda, Punjab," while the body of the

document is a Cameroon-based doctoral-level thesis on antituberculosis drug safety. This appears to be a template or file-labeling artifact rather than a substantive issue with the research itself, but it should be resolved before the document is submitted or cited formally.

8. Implications for Policy and Practice

The findings support several concrete recommendations, several of which the original thesis directs at specific stakeholders. For the Ministry of Public Health, the priority is structural: Cameroon's pharmacovigilance system currently rests on a single focal-point pharmacist with no dedicated PV unit, and strengthening this — through clearer standard operating procedures, dedicated staffing, and active (rather than purely passive/spontaneous) surveillance — is a prerequisite for catching safety signals like the cardiovascular findings in Study 3 before they accumulate unnoticed. For the National Tuberculosis Program specifically, routine annual reporting should be expanded beyond treatment success rates to include systematic ADR and persistence tracking, and an active drug-safety monitoring (aDSM) system should be implemented specifically for MDR-TB regimens, consistent with WHO's own aDSM framework.

For clinicians, the most immediate, low-cost intervention is correcting the weight-based dosing non-conformities identified for moxifloxacin and clofazimine in Study 3, alongside establishing systematic ECG/QT monitoring for any patient on concurrent bedaquiline, clofazimine, and moxifloxacin. For technical and financial partners funding TB programs, the thesis's central caution is that safety data generated in other countries cannot be assumed to transfer directly to Cameroon's population, given differences in demographic, genetic, nutritional, and comorbidity profiles (notably the high HIV co-infection rate observed in these cohorts) — meaning pharmacovigilance capacity should be funded as a core component of MDR-TB programs, not an optional add-on.

9. CONCLUSION

This review has synthesized three linked studies tracing the safety and utilization profile of MDR-TB treatment in Cameroon from 2017 to 2023. The evidence shows that the 2020 WHO shift from aminoglycosides to bedaquiline successfully resolved the dominant safety problem of the prior regimen — ototoxicity — and substantially improved treatment persistence during the intensive phase. At the same time, it surfaced a new and clinically significant concern around cardiovascular safety, particularly QT-interval prolongation risk from

the combined use of bedaquiline, clofazimine, and moxifloxacin. Across all three studies, persistence during the ambulatory continuation phase and the near-total absence of national-level ADR reporting emerge as the most pressing unresolved gaps. As MDR-TB treatment regimens continue to evolve globally, this body of work makes the case that each efficacy-driven guideline revision must be paired with a proportionate investment in active, country-specific pharmacovigilance — without which, safety improvements achieved on paper may not translate reliably into safety improvements at the bedside.

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