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Evidence Based Case Report: Comparison of Fixed-Dose Combinations Vs Separate Combinations of First-Line Antituberculosis Drugs in Patients With Drug-Sensitive Pulmonary Tuberculosis and Obesity

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ABSTRAK

Pulmonary tuberculosis (TB) remains a global health problem, while obesity has the potential to affect the pharmacokinetics of rifampicin and the effectiveness of therapy. Although the WHO recommends a fixed-dose combination (FDC), its effectiveness compared to a single-drug formulation (SDF) in obese patients remains controversial. This Evidence-Based Case Report aims to evaluate the efficacy and safety of FDCs compared to SDFs in obese adult patients with drug-sensitive pulmonary TB. A literature search was conducted in PubMed, Cochrane, and Scopus, yielding four studies that met the criteria (three randomized controlled trials and one cohort study). A critical review revealed mixed results, with some studies supporting the non-inferiority of FDCs, while others indicated a risk of less favorable clinical outcomes. Based on the available evidence, the use of SDFs is more strongly recommended for obese patients with a suboptimal response to FDCs, as this approach has the potential to reduce the risk of underdosing and treatment failure through more optimal monitoring of dosage and clinical response.

1. INTRODUCTION

Tuberculosis (TB) remains one of the leading causes of death from infectious diseases worldwide. According to the Global Tuberculosis Report 2025 published by the World Health Organization (WHO), an estimated 10.7 million people developed TB and 1.23 million died from the disease in 2024 (WHO, 2025). Indonesia accounts for approximately 10% of the global TB burden and is among the eight countries with the highest number of TB cases worldwide (WHO, 2025). At the same time, obesity has become a global epidemic and is no longer confined to high-income countries. Its prevalence is also increasing in countries with a high burden of TB, including Indonesia, which is undergoing a double epidemiological transition characterized by a growing burden of noncommunicable diseases, including obesity, alongside persistent infectious diseases (Mendis et al., 2025). The coexistence of TB and obesity therefore represents more than the coincidental occurrence of two major health problems; it may define a clinically distinct population in whom the response to anti-tuberculosis treatment differs from that of individuals with normal body weight. In this context, obesity-related changes in the pharmacokinetics of anti-tuberculosis drugs (ATDs) may have direct implications for selecting an appropriate treatment regimen and should not be considered merely an issue of treatment adherence (Thahir et al., 2025).

Obesity can alter drug pharmacokinetics through changes in body composition, volume of distribution, and drug clearance, with potentially important clinical consequences (Wahyudin et al., 2017). Rifampicin is particularly relevant because of its lipophilic properties and the limitations of weight-based dosing. Although the recommended rifampicin dose is approximately

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8–12 mg/kg, several dosing guidelines, including WHO operational guidance, use a highest weight-band category of ≥65 kg without further stratification for patients whose body weight substantially exceeds this threshold (Prager et al., 2025). Consequently, patients with obesity who receive a fixed dose within the highest weight category may receive a progressively lower dose per kilogram as body weight increases. This may contribute to lower plasma exposure through changes in the volume of distribution and drug clearance associated with obesity (Cerezales et al., 2011; Prager et al., 2025). Suboptimal rifampicin exposure has been associated with poorer treatment outcomes, including delayed sputum conversion, treatment failure, and relapse (Ramachandran et al., 2020). Prolonged exposure to subtherapeutic drug concentrations may also increase the risk of drug resistance, in addition to the challenges associated with adherence to a treatment regimen lasting at least six months. Thus, obesity-related pharmacokinetic changes may be an important determinant of treatment response alongside conventional factors such as treatment adherence.

For drug-susceptible pulmonary TB, the standard first-line regimen consists of four drugs—isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)—administered during the intensive phase for two months, followed by isoniazid and rifampicin during the continuation phase for four months (WHO, 2022). These drugs can be administered as fixed-dose combinations (FDCs) or as separate drug formulations (SDFs). FDCs offer several practical advantages, including a simpler treatment regimen, a reduced pill burden, and a lower risk of selective non-adherence to individual drugs, which may contribute to the development of drug resistance (Blomberg et al., 2001). Accordingly, WHO recommends FDCs as an option for supporting the management of TB treatment (WHO, 2022). However, much of the evidence supporting FDC use has been derived from populations that do not specifically represent patients with obesity. This raises an important clinical question: whether the pharmacokinetic and clinical advantages of FDCs remain applicable to patients with obesity, whose drug distribution and elimination may differ from those of individuals with normal body weight.

Evidence regarding the clinical equivalence of FDCs and SDFs in patients with obesity remains limited and inconsistent. Some studies have reported lower rifampicin bioavailability with FDCs than with separate drug formulations, raising concerns about inadequate drug exposure and potentially poorer treatment outcomes (Agrawal et al., 2004). In contrast, other studies and systematic reviews conducted in the general TB population have reported comparable efficacy and safety between FDCs and SDFs. These discrepancies may reflect differences in study populations, the quality and dissolution characteristics of FDC formulations, outcome measures, and nutritional status. Importantly, most previous studies have not specifically included or stratified patients with obesity, and pharmacokinetic outcomes have not always been linked to clinically relevant outcomes such as treatment success, sputum conversion, relapse, adverse drug reactions, and mortality. To date, direct comparative evidence evaluating these clinical outcomes between FDCs and SDFs in adults with obesity and drug-susceptible pulmonary TB remains scarce. This represents an important evidence gap because this population may be particularly vulnerable to obesity-related pharmacokinetic alterations.

The existing clinical guidelines also reflect this uncertainty. A recent review of ATD pharmacokinetics in overweight and obese populations suggested that FDCs may not be appropriate for some patients with obesity and proposed individualized dosing guided by therapeutic drug monitoring (TDM) (Prager et al., 2025). However, this recommendation is primarily based on expert interpretation of the available literature rather than direct comparative clinical evidence. Moreover, routine TDM is not readily available in many healthcare settings, particularly in resource-limited settings such as Indonesia. Consequently, clear recommendations regarding the preferred OAT formulation for patients with obesity remain limited. In clinical practice, this creates a genuine therapeutic dilemma when clinicians must choose between FDCs and SDFs for obese patients with drug-susceptible pulmonary TB without population-specific evidence to guide the decision.

This clinical uncertainty provides a rationale for an Evidence-Based Case Report (EBCR). Rather than generating new primary data, an EBCR integrates the best available scientific evidence with the clinical characteristics and treatment needs of an individual patient. This

approach is particularly relevant when evidence for a specific patient population is limited and an immediate clinical decision is required. In this report, current evidence comparing the effectiveness and safety of FDCs and SDFs will be critically appraised, with particular attention to treatment success, sputum conversion, relapse, adverse drug reactions, and mortality.

The primary objective of this evidence-based case report is to determine whether FDCs provide comparable or superior effectiveness and safety to SDFs in patients with drug-susceptible pulmonary TB and obesity, thereby supporting a rational, evidence-based decision regarding the selection of an appropriate OAT formulation. The novelty of this report lies in its specific focus on the available evidence concerning drug-susceptible pulmonary TB in patients with obesity, a population for which clinical and pharmacokinetic evidence remains considerably more limited than that available for patients with normal body weight or underweight. By integrating the available evidence with the clinical context of an obese patient with pulmonary TB, this report aims to provide clinically relevant guidance for treatment selection in this population.

2. METHOD

A literature search was conducted using three medical databases: PubMed, Cochrane Library, and Scopus. The search strategy used a combination of keywords related to tuberculosis, drug formulations, and obesity, including tuberculosis, pulmonary tuberculosis, fixed-dose combination, combined formulation, combination pill, single drug, separate drug, individual drug, loose drug, single formulation, and obesity. The keywords were combined using Boolean operators to identify relevant studies addressing the use of FDCs and SDFs in patients with tuberculosis and obesity.

Studies that met the eligibility criteria were subsequently selected for critical appraisal. The inclusion criteria were: (1) studies involving adults with obesity and tuberculosis who received treatment with FDCs and/or SDFs and reported at least one relevant clinical outcome, including treatment success or cure, relapse, adverse drug reactions, or treatment adherence; and (2) studies with a randomized controlled trial (RCT) or cohort study design. Studies were excluded if they were duplicates identified across databases, published in languages other than English, unavailable as full-text articles, or did not specifically evaluate FDCs and/or SDFs in the target population. Studies that did not report relevant clinical outcomes were also excluded.

Table 1. Literature Search Strategy

Database		Search Strategy	Hits
PubMed	#1	(Tuberculosis OR tuberculosis pulmonary AND "Fixed-Dose Combination“ OR "combined formulation“ OR "combination pill“ AND "single drug“ OR "separate drug“ OR "individual drug“ OR "loose drug“ OR "single formulation“ AND obesity) Filters: Free full text	67
Scopus	#1	Tuberculosis OR tuberculosis pulmonary AND "Fixed-Dose Combination“ OR "combined formulation“ OR "combination pill“ AND "single drug“ OR "separate drug“ OR "individual drug“ OR "loose drug“ OR "single formulation“ AND obesity Filter : 2015-2025, Article, English, Isoniazid, Rifampicin, Ethambutol, Pyrazinamid, Antitubercular agent, Tuberculostatic agent, single drug dose, fixed-dose combination	13
Cochrane	#1	tuberculosis	9462
	#2	("Fixed-Dose Combination")	3348

	#3	(FDC)	1512
	#4	("combined formulation")	63
	#5	("combination pill")	90
	#6	#2 OR #3 OR #4 OR #5	3864
	#7	("single drug")	10155
	#8	("separate drug")	26
	#9	("individual drug")	218
	#10	("loose drug")	2
	#11	("single formulation")	31
	#12	#7 OR #8 OR #9 OR #10 OR #11	10424
	#13	#1 AND #6 AND #12 AND obesity	20
Hand searching		The analysis was conducted on the studies that met the eligibility criteria	4

3. RESULT AND DISCUSSION

Result

The literature search conducted across the three databases using the predefined search terms identified a total of 67 records. After removing duplicate records, 48 unique articles remained, with 19 duplicates identified across the databases. The remaining articles were screened based on the predefined eligibility criteria, including population, intervention, comparison, study design, and relevant outcomes. During the screening process, articles were excluded if they did not meet the specified eligibility criteria. Additional filters were applied, including publication year (2015–2025), English language, appropriate intervention, and relevant clinical outcomes. Following the screening and eligibility assessment, four studies were included in the final critical appraisal: three randomized controlled trials (RCTs) and one cohort study. The flow of the literature search and study selection process is presented in Figure 1.

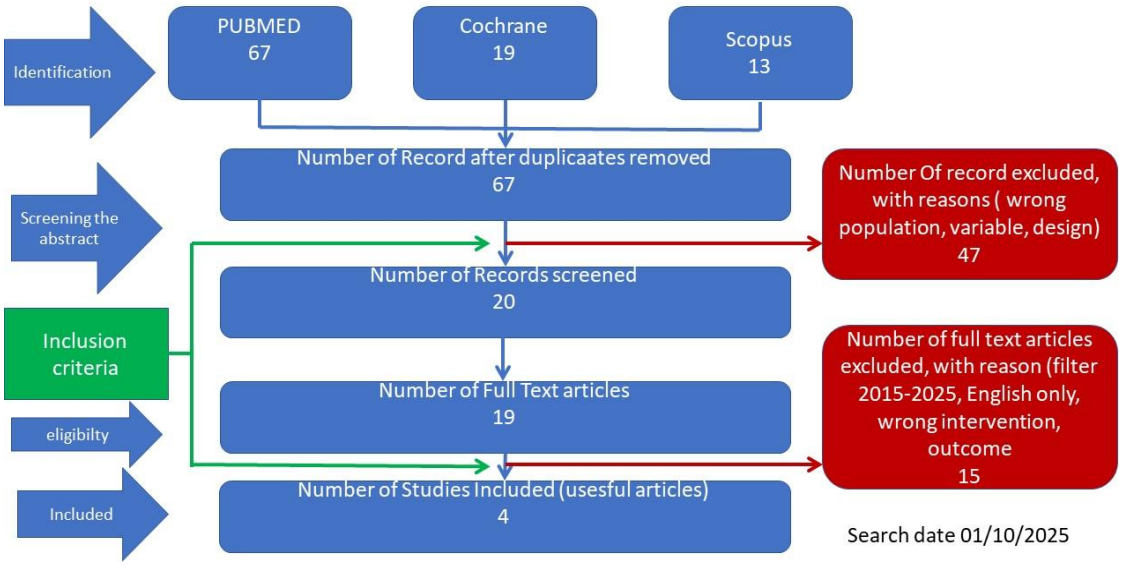

Figure 1. Literature Search and Study Selection Flowchart

The included studies had similar characteristics in terms of population, intervention, comparison, and outcomes. The study populations consisted of adult patients with tuberculosis. The intervention evaluated in all four studies was the use of a fixed-dose combination (FDC), while the comparison group received separate drug formulations (SDFs). Thus, the intervention and comparator were consistent across the included studies. The four included studies also reported comparable clinical outcomes, including treatment cure, treatment success, treatment adherence, and adverse drug reactions. A summary of the characteristics of the studies that met the eligibility criteria and were included in the critical appraisal is presented in Table 2.

Table 2. Characteristics of the Included Studies

Peneliti dan Tahun	Desain Studi	n	*Population*	*Intervention*	*Comparison*	*Outcome*	*Level of Evidence*
Aseffa, *et al.* 2016	RCT	1000	Adults newly diagnosed with culture-positive Pulmonary Tuberculosis (PTB)	Fixed-dose combination (FDC) TB treatment regimens	Loose formulation (LF) TB treatment regimens	*Kesembuhan mikrobiologis (mITT analysis)*	1b
Nazari, *et al.* 2021	RCT	331	positive sputum smear pasien, new TB case, weight over 30 kg, age over 13 years, possibility of short-course treatment under observation, and absence of diabetes, immune deficiency, or liver/kidney disease	Fixed-dose combination (FDC).	Regimen obat terpisah.	*Keberhasilan pengobatan akhir* *Kejadian Efek Samping*	1b
Khodakarim, *et al.* 2020	RCT	331	Patients smear-positive, new cases, weighed over 30 kg, were over 13 years old, and could receive short-course treatment under observation	Fixed-dose combination (FDC).	Regimen obat terpisah.	*Konversi sputum pada bulan ke-2*	1b

Lai, et al 2019	Cohort	11,489	pulmonary tuberculosis patients prescribed with FDC or EHRZ, aged ≥15, and having a positive initial sputum smear	Fixed-dose combination (FDC)	Regimen obat terpisah (EHRZ).	*Konversi sputum pada bulan ke-2 dan ke-6.* *Hasil pengobatan (kepatuhan, kegagalan, keberhasilan, kematian).*	2b

The studies included in this EBCR had generally appropriate methodological characteristics. All four studies used a two-arm design, with an active control group as the comparator. Three studies used random allocation, whereas one study used matching with natural allocation rather than a predetermined allocation procedure. The baseline characteristics of the participants were generally comparable between the intervention and comparison groups. However, some differences in baseline characteristics were identified across the included studies. Two studies reported comparable treatment allocation and equal sample sizes between the intervention and comparison groups. In one study, the observation period and sex distribution differed significantly between groups. Another study used a matching approach without predetermined allocation. These methodological differences were considered when interpreting the findings of the included studies.

Table 3. Results of the Critical Appraisal

Artikel	Was the assignment of patients to treatments randomised?	Were the groups similar at the start of the trial?	Aside from the allocated treatment, were groups treated equally?	Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	How large was the treatment effect?	How precise was the estimate of the treatment effect?
Aseffa, et al [8]	Randomised: Yes Arm: 2 Active Control	Yes Allocation= 1:1	Yes	Yes	Yes Single-blind	Microbiological cure (mITT analysis) EER: 398/459 = , 0.867 CER: 396/465 = 0.852. RR: 0.867/0.852 = 1.02 ARR: 0.867 - 0.852 = 0.015. NNT: 1/0.015 ≈ 67	The CI did not cross the prespecified non-inferiority margin, demonstrating that FDC was non-inferior to SDF.
Nazari, et al [9]	Randomised: Yes Arm: 2	Yes Allocation= 1:1	Yes	Yes	Yes Objective assessment,	Final treatment success	Statistically significant result (P = 0.03)

	Active Control				but not blinded	EER: 126/141 = 0.894, CER: 132/138 = 0.957. RR: 0.894/0.957 = 0.934 ARR: 0.894 - 0.957 = -0.063 NNT: 1/0.063 ≈ 16 Adverse effects: Adj. IRR = 3.39, P = 0.043 EER: 15/168 = 0.893, CER: 3/161 = 0.186. RR: 0.0893/0.0186 = 4.80 ARR: 0.0186 - 0.0893 = -0.0707 NNT: 1/0.0707 ≈ 14	FDC 6.3% Less effective Adverse effects: Adj. IRR = 3.39, P = 0.043 Patients receiving FDC had a 4.8-fold higher risk of experiencing adverse events
Lai, et al[11]	Yes Arm: 2 Active control	Yes (after matching) Allocation= Not specified (natural allocation)	Unclear	Yes	Yes Objective assessment, but not blinded	Sputum conversion at month 2 EER: 4033/4188 = 0.963 CER: 3949/4188 = 0.943 RR: 0.963/0.943 = 1.021 ARR: 0.963 - 0.943 = 0.02 NNT: 1/0.02 = 50	FDC was 2% more effective, with a number needed to treat (NNT) of 50 to achieve one additional sputum conversion at month 2.

Table 4. Applicability of the Study Findings to the Case

Article RCT	Is my patient so different to those in the study that the results cannot apply?	Is the treatment feasible in my setting?	Will the potential benefits of treatment outweigh the potential harms of the treatment for my patients	Result
Aseffa, et al	No	Yes	Yes	Applicable
Nazari, et al	No	Yes	No (harm)	Applicable
Lai, et al	No	Yes	Yes	Applicable

Tabel 5. Perbandingan effect size.

No	Effect size	Aseffa, et al	Nazari, et al	Lai, et al
1	RR	1.02	0.934 (Final treatment success) 4.80 (Adverse drug reactions)	1.021
2	ARR	0.015	−0.063 (Final treatment success) −0.0707 (Adverse drug reactions)	0.02
3	NNT	67	-	50
4	ARI	-	0.063 (Final treatment failure) 0.0707 (Adverse drug reactions)	-
5	NNH	-	16 (Final treatment failure) 14 (Adverse drug reactions)	-

Discussion

The critical appraisal of the four relevant studies demonstrated substantial variation in the quality and applicability of the available evidence. Aseffa et al. (2016) represented the highest level of evidence among the included studies, using a randomized controlled trial (RCT) with several important methodological strengths. The study employed a single-blind design, centrally controlled computerized randomization through WHO/TDR, allocation concealment using sealed envelopes, and a modified intention-to-treat analysis. However, the applicability of its findings to the present case is limited by serious indirectness. Only approximately 2% of participants were overweight or obese, whereas the patient in the present case had a body mass index (BMI) >30 kg/m^2. Therefore, although the study provides relatively robust evidence regarding the general TB population, its findings cannot be directly extrapolated to patients with obesity.

Hashemi Nazari et al. (2021) also used an RCT design, providing a relatively high level of evidence. Nevertheless, several methodological limitations were identified. The study did not clearly report the blinding procedures for participants or outcome assessors, potentially increasing the risk of performance and detection bias. In addition, 52 participants (15.7%) were lost to follow-up, and the reasons for loss were not fully described. These limitations may reduce confidence in the internal validity of the findings. Despite these concerns, the study reported statistically significant differences in several clinically relevant outcomes, including adverse events and treatment failure.

Lai et al. (2019) provided real-world evidence from a large cohort of 8,376 participants. The large sample size increased the statistical precision of the estimates, while propensity score matching was used to reduce baseline differences between treatment groups. However, as an observational study, residual confounding cannot be completely excluded. The findings should therefore be interpreted in light of the potential influence of unmeasured factors that may have affected treatment selection and clinical outcomes.

The effect estimates varied considerably across the included studies. Aseffa et al. (2016) reported a risk difference of 1.5% (90% CI, −2.2% to 5.3%), with the confidence interval remaining within the prespecified non-inferiority margin of 4%. These findings supported the non-inferiority of FDC compared with separate drug formulations in the studied population. However, the clinical applicability of this result to patients with obesity remains uncertain because the study population contained very few participants with overweight or obesity. The small absolute difference between treatment groups should therefore not be interpreted as evidence that FDC provides an additional clinical benefit in patients with obesity.

In contrast, Hashemi Nazari et al. (2021) reported an absolute risk increase of 7.07% for adverse events, corresponding to a number needed to harm (NNH) of approximately 14, and an absolute risk increase of 6.29% for treatment failure, corresponding to an NNH of approximately 16. Although confidence intervals were not fully reported, the observed differences were

statistically significant, with $P = 0.043$ for adverse events and $P = 0.03$ for treatment failure. These findings raise clinically relevant concerns regarding the comparative performance of FDC in the population studied. However, because the study did not specifically focus on patients with obesity, these findings should not be interpreted as evidence that FDC is inherently inferior in obese patients.

The direction and magnitude of treatment effects also varied across studies. Aseffa et al. (2016) demonstrated non-inferiority of FDC, whereas Hashemi Nazari et al. (2021) reported poorer outcomes with FDC for several endpoints. Lai et al. (2019) provided additional evidence from a large observational population. The differences between studies may be related to variations in patient characteristics, treatment settings, adherence, program implementation, drug formulations, and other unmeasured factors. Differences in the pharmacokinetic properties and bioavailability of FDC products may also contribute to variability in treatment exposure. However, these explanations remain hypotheses and should not be considered established causes of the observed differences.

The subgroup findings reported by Hashemi Nazari et al. (2021) are of particular clinical interest because they suggested poorer outcomes among patients with suboptimal treatment responses. This finding is relevant to the present case, in which the patient remained sputum smear-positive (+2) after one month of FDC therapy. Nevertheless, the similarity between the study findings and the clinical course of the present patient should be interpreted cautiously. The available evidence does not establish that the patient's suboptimal response was caused by the use of FDC. Other potential explanations, including adherence, baseline disease severity, bacterial burden, drug susceptibility, drug absorption, comorbidities, and other patient-related factors, should also be considered.

A major limitation of the current evidence is the lack of studies specifically evaluating obese patients with drug-susceptible pulmonary TB. The studies included in this EBCR were largely conducted in populations with average body weights substantially lower than that of the present patient, and none provided a sufficiently powered analysis specifically for patients with BMI >30 kg/m^2. Consequently, the extent to which the reported treatment effects apply to obese patients remains uncertain.

Obesity may alter the pharmacokinetics of anti-tuberculosis drugs through changes in body composition, volume of distribution, hepatic metabolism, and drug clearance. Rifampicin and isoniazid may be particularly relevant because variability in drug exposure has been reported among individuals with different body compositions. These pharmacokinetic considerations provide a plausible rationale for concern about inadequate drug exposure in some patients with obesity. However, pharmacokinetic variability alone does not establish that FDCs result in clinically inadequate exposure or poorer treatment outcomes in all obese patients.

In the present case, the persistence of a positive sputum smear after one month of treatment represents a suboptimal early response that warrants further clinical evaluation. The use of separate drug formulations may offer greater flexibility for individualized dose adjustment than FDCs. However, changing the formulation solely on the basis of obesity and early sputum positivity should be approached cautiously. Before modifying the treatment regimen, other causes of suboptimal response should be evaluated, including adherence, drug susceptibility, drug-drug interactions, malabsorption, disease severity, and the possibility of inadequate drug exposure. Where available, therapeutic drug monitoring may provide additional information regarding individual drug exposure.

Based on the available evidence, FDC cannot be considered definitively superior or inferior to SDF in patients with obesity. The evidence supporting FDC non-inferiority primarily comes from populations that do not adequately represent obese patients, while evidence suggesting poorer outcomes with FDC also lacks specific validation in this population. Therefore, the decision to use FDC or SDF should be individualized according to the patient's clinical characteristics, treatment response, adherence, drug susceptibility, potential drug interactions, and the availability of therapeutic drug monitoring.

For patients with obesity who initiate treatment for drug-susceptible pulmonary TB, FDC may remain a reasonable treatment option when recommended dosing can be achieved and close clinical monitoring is available. Particular attention should be given to treatment response, sputum conversion, adherence, and the occurrence of adverse drug reactions. If the patient demonstrates a suboptimal response, a comprehensive reassessment should be undertaken before considering a change to separate drug formulations. SDF may be considered when individualized dose adjustment is clinically indicated or when there are concerns regarding inadequate drug exposure.

Several important evidence gaps remain. First, none of the included studies specifically evaluated adults with obesity and drug-susceptible pulmonary TB. Second, the available studies did not provide adequately powered subgroup analyses according to BMI or body weight. Third, pharmacokinetic evidence regarding FDCs in patients with obesity remains limited, particularly concerning the relative exposure of individual components within fixed-dose formulations. Fourth, evidence regarding optimal dosing strategies for obese patients remains insufficient for both FDC and SDF regimens.

Future studies should therefore prioritize pharmacokinetic and pharmacodynamic investigations to determine optimal anti-tuberculosis drug exposure in patients with obesity. Well-designed RCTs directly comparing FDC and SDF in obese patients with drug-susceptible pulmonary TB are also needed, with clinically relevant outcomes such as treatment success, sputum conversion, relapse, adverse drug reactions, and mortality. Such studies would provide more definitive evidence to guide treatment selection in this increasingly important patient population.

4. CONCLUSION

Based on the synthesis of the available evidence and the clinical characteristics of Mr. A, an obese man (BMI >30 kg/m^2) with drug-susceptible pulmonary tuberculosis who demonstrated a suboptimal early response (sputum smear grade $+2$ after one month of FDC therapy), the available evidence does not provide sufficient certainty to establish the superiority of either FDC or separate drug formulations (SDFs) in patients with obesity. Although Hashemi Nazari et al. reported higher risks of adverse events (NNH $= 14$) and treatment failure (NNH $=$ 16) with FDC, these findings were not specifically derived from an obese population and should therefore be interpreted with caution.

In Mr. A's case, the persistence of a positive sputum smear after one month warrants comprehensive reassessment before modifying the treatment regimen. This should include evaluation of treatment adherence, drug susceptibility, potential drug interactions, gastrointestinal absorption, disease severity, and the possibility of inadequate drug exposure. Given the potential for obesity-related pharmacokinetic variability and the greater flexibility of SDFs for individualized dose adjustment, a transition to separate drug formulations may be considered if inadequate drug exposure or the need for individualized dosing is suspected. If SDF is selected, dosing should follow the applicable TB treatment guidelines and be accompanied by close monitoring of sputum conversion, treatment response, and adverse drug reactions. Overall, the decision should be individualized, as current evidence remains insufficient to conclude that FDC is inherently unsafe or ineffective in patients with obesity.

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