The antibacterial activity of metformin-containing anti-TB treatment in patients with newly diagnosed sputum smear-positive pulmonary TB, focusing on the time to sputum conversion.

Dr. Ipsita Samantaray[1*], Dr. Sashi Bhushan Biswal[2], Dr. Sudarshan Pothal[3], Dr. Baijayanti Rath[4], Dr. Devasish Panda[5], Dr. Bhabagrahi Rath[6]

[1]*Asst. Professor, department of Pharmacology,VIMSAR, Burla*
[2]*Professor, Dept of Pharmacology, VIMSAR, Burla*
[3]*Professor and HOD, Dept of Pulmonary Medicine, SJMCH, Puri*
[4]*Asst Professor, Dept of Pharmacology, PRM MCH,Baripada*
[5]*Asst Professor, Dept of Preventive and Social Medicine, BBMCH,Balangir*
[6]*Professor and HOD, Dept of Pharmacology, VIMSAR, Burla*

Corresponding author- Dr. Ipsita Samantaray
ipsita4july@gmail.com

Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

Abstract:
Background: New drug-resistant tuberculosis (TB) strains and the need for innovative treatments have led to the disease's resurgence as a public health concern. Patients may struggle to adhere to traditional anti-tubercular treatments (ATT) for up to six months, and there's a risk of drug toxicity. **Aim:** To study the antibacterial activity, in terms of time to sputum conversion of metformin-containing anti-TB treatment(ATT) regimen instituted during the initial 8 weeks of treatment in patients withnewly diagnosed sputum smear-positive pulmonary TB. **Materials & methods:** The VIMSAR, Burla, Department of Pharmacology and Pulmonary Medicine conducted a controlled, parallel arm, randomized clinical trial from 2018 to 2020, targeting adult non-diabetic patients with pulmonary tuberculosis and acid-fast bacilli. The study included 75 patients randomly assigned to either the control or metformin group, with baseline investigations and blood tests. **Results:** The study involved sputum smear examinations and found that a significant proportion of patients in the metformin group achieved smear negativity compared to the control group. After the intensive phase, one patient in the metformin group remained sputum positive, while 12 in the control group remained sputum propitious. Drug susceptibility testing using the GeneXpert system revealed that one patient in the metformin group was resistant to Rifampicin, while the control group's six patients showed sensitivity to the standard ATT, leading to continued use of the same medications. **Conclusion:** The study suggests that adding metformin to pulmonary TB treatment may shorten sputum conversion time, enhance immune response, accelerate bacterial clearance, and reduce transmission rates. However, further research is needed to determine optimal dosage and patient populations for optimal metformin benefits.

Key words: Mycobacterium tuberculosis; anti-tubercular treatment; Immunomodulatory; Resistance; Metformin; Sputum smears.
How to cite this article: Samantaray I, Biswal SB, Pothal S, Rath B, Panda D, Rath B. The antibacterial activity of metformin-containing anti-TB treatment in patients with newly diagnosed sputum smear-positive pulmonary TB, focusing on the time to sputum conversion. Int J Drug Deliv Technol. 2026;16(63s):415-420. DOI: 10.25258/ijddt.16.63s.44
Source of support: Nil.
Conflict of interest: None

Introduction:

New drug-resistant tuberculosis (TB) strains and the need for innovative supplementary treatments to supplement existing TB treatments have contributed to the disease's comeback as a public health concern. Patients may have trouble sticking to their traditional anti-tubercular treatment (ATT) regimens for as long as six months, and there's also the risk of drug toxicity. The usage of adjunct treatments, especially metformin, to enhance the efficacy of ATT has recently attracted more attention in this setting, according to the available studies. In addition to its main function in glucose management, the widely used antidiabetic drug metformin may have immunomodulatory and host-directed effects that help in the battle against tuberculosis [1,2].

Metformin is a biguanide-class medicine that can help the body fight TB infections. It does this by changing

the production of cytokines and making macrophages work better [3]. According to Sharma et al. [4], the main idea is that metformin could improve host-directed immunity and autophagy, which would make it better at managing the bacterial load in macrophages. These supplementary treatments play a crucial role in accelerating the reduction of bacterial load and, by restricting the duration of antibiotic exposure, potentially reducing the development of resistance. The critical need for therapeutic options that can reduce the duration of tuberculosis medication or enhance sputum conversion times makes research on the use of metformin in tuberculosis treatment extremely pertinent to world health.

A key milestone in the treatment of pulmonary tuberculosis is sputum conversion, which is defined as the change from sputum smear-positive to sputum smear-negative status. This change indicates a reduction in infectiousness and is associated with positive clinical outcomes. Sputum conversion occurs in most smear-positive patients after two months of starting ATT; hence, any factors that help speed up this conversion should be useful in improving tuberculosis management [5]. As an addition to standard ATT, metformin has been tested repeatedly to see if it can improve bacterial results and boost the immune system [6,7]. A study [8] found clinical evidence that metformin can greatly improve the host immunological response, which may result in faster sputum conversion rates in patients taking ATT.

In order to reduce bacterial burdens and avoid transmission, the first eight weeks of rigorous ATT are particularly important. The introduction of metformin at this phase has the potential to improve treatment efficacy by decreasing the duration of infectiousness and the danger of community transmission [8]. This is because it shortens the time to sputum conversion. In addition, metformin may have a double advantage of lowering blood sugar levels and speeding up the healing process of tuberculosis in groups where both diseases are common, such as those with diabetes [9-11].

In patients with newly diagnosed pulmonary tuberculosis who tested positive for sputum smears during the crucial first eight weeks of treatment, this study aims to examine the effects of an ATT regimen that includes metformin on the time it takes for sputum to convert into a usable form. Looking into how well metformin works in ATT regimens could help improve TB management strategies. This could lead to shorter treatment times and better results because it affects the immune system and may change the consistency of sputum. Optimal and personalized treatment strategies for impacted communities will depend on our understanding of adjunct medications like metformin, as TB continues to be a global health concern. Hence, present aim was to study the antibacterial activity, in terms of time to sputum conversion of metformin-containing ATT regimen instituted during the initial 8 weeks of treatment in patients withnewly diagnosed sputum smear-positive pulmonary TB.

Materials & methods:

The Institutional Human Ethics Committee approved the investigation, adhering to ICH Good Clinical Practice and ICMR ethical guidelines. The Declaration of Helsinki's principles ensured the rights, safety, and well-being of study subjects. Confidentiality was maintained, and only essential personal data was processed for investigating antibacterial activity, safety, and tolerability of the investigational product.

The research was conducted by the Department of Pharmacology and the Department of Pulmonary Medicine at VIMSAR, Burla, over a 24-month period from October 2018 to October 2020. The study was a controlled, parallel arm, randomized clinical trial with an open label. The study was open to adult non-diabetic patients, previously untreated, newly diagnosed with pulmonary tuberculosis, and with a positive sputum smear sample for acid-fast bacilli. The sample size was 150, and 75 patients were randomly assigned to either the control group or the method of meeting group. Before initiating the study, baseline investigations were conducted on all patients diagnosed with sputum smear-positive pulmonary tuberculosis. Blood tests included hemoglobin, total red blood cell, total white blood cell, differential count, and platelet count. Patients who met the inclusion criteria expressed willingness to participate, and did not exhibit rifampicin resistance signed an enrollment consent form.

The study randomly assigned 75 patients to either the control group or the metformin group. All patients were administered sputum testing for M. tuberculosis by light microscopy on a weekly basis during the initial two months of treatment. Patients who were either ineligible or unwilling to participate in the study were referred to the national program for treatment in accordance with current guidelines. The control group received standard tuberculosis treatment (A TT) for the first two months, followed by isoniazid, rifampicin, pyrazole, and ethambutol for the subsequent four months. The Metformin group received Metformin 500 mg once daily, after food, for six months, in addition to the standard ATT.

Subsequent evaluations included weekly sputum smear examinations, monitoring blood sugar levels after two months of insulin therapy, using GeneXpert (CBNAAT) to detect drug resistance patterns after a two-month intensive phase, and assessing adverse events and tolerability. Patients were advised to undergo follow-up appointments every week for the first two months and then once every 15 days after

that. The study involved patients who were drug-sensitive and had their sputum tested weekly until it turned negative. They continued to receive the same treatment after the intensive phase, and if their sputum remained positive, they were excluded. The study investigated whether they developed drug resistance at the conclusion of the intensive phase, repeating all blood parameters and documenting adverse events and tolerance during each subsequent appointment. Drug sensitivity testing was conducted using GeneXpert and/or LPA at the conclusion of the intensive phase.
Treatment delivery, compliance, and retention were monitored by study personnel, who emphasized the importance of adhering to the treatment schedule at each visit. Treatment supporters and enablers facilitated the retention of the study participants, and a dedicated DOTS provider administered the treatment in an ambulatory manner. Treatment adherence was assessed through evaluations of the treatment card and unfilled pill covers in case of drug supply disruptions.

The trial involved concurrent administration of medications, with the use of non-antibiotic drugs permitted in tiny quantities. The investigator administered only those medications deemed essential for the subject's well-being and unlikely to interfere with the study medication. Potential reasons for withdrawal included pregnancy, the investigators' belief that the patient's continued participation would be detrimental to their health, the patient's failure to adhere to study procedures or their refusal to attend appointments, or the patient's desire to withdraw for any reason.

Results of the investigation included the length of time between the start of treatment and the acquisition of the negative smear. Blood tests were conducted at the conclusion of six months, including hemoglobin, total red blood cells, total white blood cells, differential count, platelet count, liver function tests, and kidney function tests. The safety and tolerability analysis encompassed all patients who were randomly assigned to and received at least one dose of the study regimen. The study improved disease status by reducing symptoms, signs, and conversion of sputum smears while ensuring the safety and tolerability of the treatment in terms of adverse events (AEs) in both the clinic and the lab. The investigator and teams supervised the secure storage of all critical trial documents under lock and key at the recruiting sites.

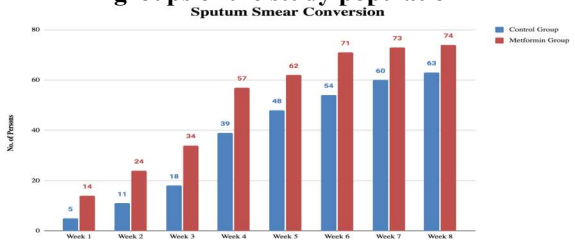
Statistical analysis:

Statistical analyses were conducted using SPSS version 25.0. Descriptive statistics, such as percentages, were used to analyze the variable distribution. A paired t-test was used to compare the means, and Chi-square was used to identify the association. P <0.05 was considered significant.

Results:

The 24-month study period yielded the following observations: Demographic information: 150 patients with newly diagnosed pulmonary tuberculosis participated in the study, with 10 patients (5 from each cohort) lost to follow-up. A total of 107 patients were male and 43 were female. In the control group there were 56 males and 19 females, while in the metformin group there were 51 males and 24 females. The p value of more than 0.05 in the chi square test demonstrated that there was no significant difference in the gender distribution of the patients between the two groups.
In the control group, the mean age of the patients was 39 ±11.6 years, while in the Metformin group, it was 42 ±12.7 years. The age distribution of the patients between the two groups did not exhibit any significant difference, as indicated by the p value of more than 0.05 in the unpaired t-test. Therefore, both groups were comparable in terms of gender and age.

Figure 1: Sputum smear Conversion in both groups of the study population



We conducted sputum smear examinations at baseline and on a weekly basis until the results were negative (Figure 1). A substantial proportion of patients in the metformin group achieved smear negativity in comparison to the control group, as evidenced by the weekly sputum smear test. After the conclusion of the intensive phase (IP), one patient in the metformin group remained sputum positive, while 12 patients in the control group remained sputum propitious. The metformin group demonstrated a substantially shorter average time for sputum smear conversion than the control group (p = 0.012, unpaired t-test). In the metformin group, the duration was approximately 3.59 ±1.74 weeks, while in the control group, it was 4.26 ±2.31 weeks.
At the end of the intensive phase, we conducted drug susceptibility testing using the GeneXpert system for patients who remained sputum positive in both groups (Table 1). One of the patients in the metformin group who continued to have sputum positives was resistant to Rifampicin. Out of the 12 patients in the control group who remained sputum positive, 4 were resisting Rifampicin, and 2 had indeterminate results in GeneXpert. LPA analyzed the sputum of the patients with an indeterminate result in GeneXpert and found

them to be INH-resistant. The control group's six additional sputum-positive patients showed sensitivity to the standard ATT, leading to their continued use of the same medications until their sputum turned negative. The results showed a statistically significant difference in the development of drug resistance (p-value = 0.0047, chi square test).We excluded the drug-resistant patients from the study and prescribed them suitable alternative drug regimens.

Table 1: Drug resistance pattern in both groups of the study population.

Drug Resistance	Control Group	Metformin Group	Control Group (%)	Metformin Group (%)	p-value
DR Cases	6	1	8.00	2.67	0.0047

Six patients (12%) in the control group and nine patients (16%) in the metformin group experienced adverse events. The difference was not statistically significant (p-value = 0.818, chi square test). All the adverse events were trivial and associated with gastrointestinal issues like nausea, vomiting, and gastritis. Antihistaminic medications successfully managed mild skin rashes and itching in two patients in the control group and one patient in the MET group.

Table 2: Adverse reactions in the present study population.

Adverse Effects	Control group	Metformin group	P-value
Vomiting	1	3	
Abdominal discomfort	4	5	0.564
Skin rash	2	1	0.317
Nausea	2	3	0.564
None	66	63	0.544

Discussion:

The present aim was to study the antibacterial activity, in terms of time to sputum conversion of metformin-containing ATT regimen instituted during the initial 8 weeks of treatment in patients with newly diagnosed sputum smear-positive pulmonary TB. In the present study there was no significant difference in the gender distribution of the patients between the two groups. There may be differences in treatment response, adherence, or outcomes based on gender in studies that look at how metformin affects anti-TB treatment outcomes, especially the time to sputum conversion. The research suggests that gender-related differences in immune response and pharmacokinetics may influence the efficacy of TB treatment [12,13]. Specifically, the immune responses of female patients to TB and adjunctive interventions may influence the conversion rates. Furthermore, the potential impact of treatment adherence, which may differ by gender due to social or economic factors, underscores the necessity of gender-balanced enrollment and analysis [14].

The age distribution of the patients between the two groups did not show any significant difference in our study. Nevertheless, the age distribution significantly influences the antibacterial efficacy of metformin-containing anti-TB treatment, particularly in terms of the duration of sputum conversion. According to research conducted between 2016 and 2024, younger patients frequently experience sputum conversion faster than their older counterparts as a result of their more robust immune responses and fewer comorbidities [15,16]. Conversely, potential complications with metformin metabolism and age-related immune senescence in older individuals may influence the efficacy of TB treatment, potentially leading to slower conversion rates [17]. These results emphasize the necessity of stratifying results by age in order to accurately evaluate the adjunctive effects of metformin across different age groups.

Additionally, the metformin group exhibited a significantly reduced average time for sputum smear conversion compared to the control group. In comparison to the control group, the metformin group experienced a shorter duration of weeks. The sputum smear conversion rate is a primary indicator of treatment efficacy in pulmonary tuberculosis, as it reflects both a decrease in bacterial burden and a decrease in patient infectiousness. Recent research has investigated the potential of metformin as an adjunct to standard ATT, demonstrating promising results in

accelerating the duration of sputum conversion. Metformin is thought to help get rid of microbes faster by boosting the immune system, especially through processes like activating macrophages and autophagy [4,18]. Faster conversion rates support improved patient outcomes by reducing TB transmission and potentially shortening treatment duration, leading to increased adherence and reduced drug resistance rates [17].

Metformin is particularly advantageous in patients with comorbid diabetes, as it may alleviate the hyperglycemia-linked immune dysfunction that can prolong bacterial persistence in the airways [7]. According to research, sputum conversion rates for diabetic TB patients who take metformin along with ATT are either the same as or better than those for non-diabetic patients who only take ATT [19]. In general, adding metformin to TB treatment seems like a good way to make it work better, especially in diabetic patients, where better conversion of sputum could have a big effect on clinical outcomes [20].

Interestingly, our study results showed a statistically significant difference in the development of drug resistance (p-value = 0.0047, chi square test).We excluded the drug-resistant patients from the study and prescribed them suitable alternative drug regimens. Drug resistance in TB treatment presents major obstacles that affect public health as well as patient results. Supporting host-directed therapy, which targets the host immune response rather than the pathogen itself, may reduce the selective pressures contributing to drug resistance. Integrating metformin into ATT regimens has shown promise in potentially addressing these challenges [8,9, 17]. Metformin may help shorten the time it takes for sputum to become mucus by improving cellular processes like autophagy and macrophage activation, which helps get rid of bacteria. Studies have shown this, even in people with drug-resistant TB strains [4,18]. Accelerating sputum conversion allows metformin to also shorten the length of bacterial exposure to antibiotics, therefore helping to lower the chance of resistance development. Though metformin does not directly target Mycobacterium tuberculosis, its immune-enhancing properties can lower the bacterial burden more rapidly, perhaps lessening the requirement for continuous use of traditional antibiotics [8,9, 19]. So, more in-depth studies on how metformin affects various drug-resistant TB strains are needed to prove its importance in resistance patterns and figure out how to use it in different TB populations [20].

Conclusion:

This study found that adding metformin to the anti-TB treatment plan for people who have just been diagnosed with sputum smear-positive pulmonary TB might shorten the time it takes for the sputum to turn into a liquid form. The adjunctive use of metformin may enhance the immune response against Mycobacterium tuberculosis, thereby accelerating bacterial clearance. Reducing the time to sputum conversion could reduce transmission rates and enhance treatment outcomes, making it a valuable addition to conventional TB therapy. Additional research is necessary to verify these results and to investigate the optimal dosage and patient populations for maximizing metformin's benefits in the management of tuberculosis.

Conflict of interest:

There is no conflict of interest among the present study authors.

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