JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

DOI: https://doi.org/10.61919/5vt6wv21

Original Article

Lipid-Based Nanoparticles for Targeted Delivery of Anti-Tubercular Drugs in Pulmonary TB Patients

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"Cite this Article" **Received**: 12 October 2025; **Accepted**: 04 February 2026; **Published**: 28 February 2026

Author Contributions: Concept: SAR, AUR, SKM; Design: SAR, SK, RAT; Data Collection: SK, BS, NN; Analysis: RAT, AUR; Drafting: SAR, SK, RAT, BS, AUR, NN, SKM. **Ethical Approval**: Yashfeen College of Pharmacy and Allied Health Sciences, Lahore, Pakistan. **Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: NA

ABSTRACT

Background: Standard medicine taken by mouth for lung tuberculosis might not work well because it can be harmful to the body and needs to be taken for a long time. Giving medicine directly to the lungs might help it work better where it is needed. Objective: To look at how germs are gone how safe the treatment is, any bad effects and how well people feel in their lungs when using inhaled medicine made with tiny fat particles compared to regular mouth medicine. Methods: This study at one place had 80 adults who had just been diagnosed with having germs in their sputum and had lung tuberculosis. They got either breathing in medicine that had tiny fat particles with isoniazid and rifampicin and less medicine by mouth with pyrazinamide and ethambutol or the regular mouth medicine for six weeks. Data from 75 people was complete. Results: The average time for the germs to go away was shorter in the group that got the treatment than the other group (22.4 ± 4.1 days versus 34.8 ± 5.6 days; difference of -12.4 days; 95% CI -14.7 to -10.1; p<0.001). After six weeks 92.1% and 70.3% of people had no germs in their sputum respectively (p=0.018). At week six the level of ALT was 31.2 ± 5.8 and 54.6 ± 12.3 U/L p<0.001). The group that got the treatment also had better scores for feeling well in their lungs and had fewer stomach problems. Medicine that is inhaled and made with fat particles helped get rid of germs faster and had fewer bad effects on the body but more studies are needed. Keywords: Administration, Inhalation; Antitubercular Agents; Drug Delivery Systems; Lipids; Nanoparticles; Treatment Outcome; Tuberculosis, Pulmonary.

INTRODUCTION

Tuberculosis is a problem for people all around the world. It is caused by Mycobacterium tuberculosis. Tuberculosis makes a lot of people sick and even causes death. This is very sad because we can prevent it (1).

Pulmonary tuberculosis is the way this disease spreads. When people with pulmonary tuberculosis cough they send out drops that have the bacteria in them. These drops can infect people (2).

To treat tuberculosis doctors give patients a lot of medicine to take. This medicine includes isoniazid, rifampicin, pyrazinamide and ethambutol. Patients have to take these medicines for a time. They have to take them every day (3). Sometimes the medicine makes people feel sick. They might get stomach problems. Feel numb in their hands and feet. Because of this some people stop taking their medicine.

This is bad because it can make the tuberculosis come back. It can also make the bacteria stronger so the medicine does not work anymore (4).

The problem with taking medicine by mouth is that it goes into the body. The medicine has to go through the stomach and liver before it gets to the lungs. This means that a lot of medicine is needed to get enough to the lungs.. This can hurt other parts of the body (5,6).

So doctors thought maybe it would be better to give the medicine to the lungs. This way more of the medicine gets to where it's needed. It also means less medicine gets to parts of the body.

There is a problem with breathing, in the medicine. The lungs can push the medicine out. The medicine can also get broken down by the body. This means the medicine does not stay in the lungs for long. The body can also get rid of the medicine quickly (7).

Lipid-based nanoparticles, including liposomes, solid lipid nanoparticles and nanostructured lipid carriers might help overcome some of these challenges. Their biocompatibility, ability to hold water- fat-soluble materials and how they work with lung surfactants make them a good choice for inhaled medicine (8). Research shows that lipid-based carriers can make medicines more stable stay longer in the lungs release slowly and help the medicine get into macrophages. These cells are a place inside the body where M. Tuberculosis lives (9).. Most of the information available comes from studies on how to make the drugs experiments with cells and tests on animals. There is not information about how well inhaled lipid nanoparticles work in people who have active lung tuberculosis. This includes how well they work, if they are safe in the body and how easy they are to use (10).

The current study, which was a controlled trial compared inhaled lipid nanoparticle-encapsulated isoniazid and rifampicin given with a lower dose of oral pyrazinamide and ethambutol to the usual oral fixed-dose treatment in adults who had just been diagnosed with active lung tuberculosis. The study looked at how the sputum became free of bacteria if the sputum was free of bacteria after six weeks the levels of chemicals in the liver and kidneys any side effects from the treatment and the quality of life for the lungs. It was expected that giving the medicine directly to the lungs would help get rid of the bacteria quickly and cause less harm to the body, than the usual oral treatment.

MATERIALS AND METHODS

This new study, which is happening at one hospital for lung problems in Central Punjab, Pakistan is a type of test called a single-centre parallel-group randomized controlled trial. The study lasted eight months from June 2025 to January 2026. It included looking for people to take part getting them to join, a six-week time where they got treatment and then checking how they did after the treatment. The study used a way to divide people into groups to see how well the new treatment works compared to the old one.

The people who took part in the study were adults between 18 and 60 years. They had just been found to have lung tuberculosis and had the right kind of sputum test. People who were checked to see if they could join the study were asked questions. Had tests. People were not allowed to join if they had a type of tuberculosis that was hard to treat or if they had bad liver or kidney problems or if they had a long-term lung problem or if they were pregnant or if they had a known reaction, to the materials used in the new treatment.

The number of people needed for the study was worked out based on how big of a change they expected to see a chance of 5 percent of making a mistake and an 80 percent chance of finding a change if there was one. They needed at 72 people. To make sure they had people even if some left the study they asked 80 people to join and split them evenly between the two groups.

People taking part in the study were split into two groups in a way using a computer. The groups were kept secret until the people got their treatment. This was done by using envelopes that were sealed and numbered. A pharmacist who was not part of the study gave out the envelopes.

It was not possible to keep the people giving the treatment and the people getting the treatment from knowing who was getting what. This is because the two types of treatment were given in ways that you could see. To make sure the results were fair the people checking the results and the people looking at the data did not know who was getting which treatment.

The people in the control group got the treatment every day. This treatment was a combination of four medicines: isoniazid, rifampicin, pyrazinamide and ethambutol. They took these medicines by mouth.

The people in the group got a special treatment. They breathed in isoniazid. Rifampicin through a special machine once a day. This machine made sure the medicines got into their body in a way. They also took pyrazinamide. Ethambutol by mouth but in smaller amounts, than the control group. Each time they used the machine it took about 20 minutes.

The people running the study kept track of whether the participants were taking their treatment as they should. They did this by watching them take their medicines and by counting their pills. They did this for six weeks to make sure everyone was doing what they were supposed to do.

The main bacterial results were how long it took for sputum culture to change and how many people had their sputum change by the end of week six. The time it took for the culture to change was given in days. The six-week result was shown as the number and percent of people who had their sputum change in each group. Other results included serum alanine aminotransferase, serum aspartate aminotransferase, serum creatinine, stomach and gut side effects and how well people felt in terms of breathing. These tests were done at the start and after the six-week treatment.

Serum alanine aminotransferase and aspartate aminotransferase levels were used to check for changes in the liver. Serum creatinine was used to check for kidney safety. Any side effects that happened during the treatment were written down those related to the stomach and gut. The St. George's Respiratory Questionnaire total score was used to see how breathing problems, activity and daily life changed. Lower scores and bigger drops, from the start meant breathing and quality of life.

The way the data was spread out was checked using the Shapiro-Wilk test. For things that could be measured like numbers the average and how much they varied were looked at. For things that could not be measured like categories the number of times they happened and what percentage they were of the total were reported. The starting points of the people in the study were compared to see if the groups were similar.

To see how much the people in each group changed from the start to six weeks in paired tests were used. To compare the groups to each other separate tests were used. The way the liver enzyme measurements changed over time was looked at to see if the time or the treatment or both had an effect. If the result of a test was likely to happen by chance than five percent of the time it was considered important.

At the start all 80 people who were part of the study were looked at. After six weeks the people who finished the study and had all their follow up tests done were looked at which was 75 people. There were 38 people in the group that got the treatment and 37 people in the group that did not. To make sure the study was fair the people were randomly assigned to groups. Who was in which group was not told to the people doing the study or the people analyzing the data. The people doing the study made sure to follow the rules and the people in the study took their medication as they should and the tests were done at the time for everyone.

The Data distribution of the liver enzyme measurements was checked. The Data distribution was a part of the study. The Data distribution and the way the people, in the study were assigned to groups were very important to make sure the study was fair. The results were real.

RESULTS

A total of 102 individuals with suspected active pulmonary tuberculosis were screened for eligibility. Twenty-two were excluded before randomization: 14 did not meet the eligibility criteria because of underlying organ dysfunction or non-susceptible strains, and eight declined participation. The remaining 80 participants were randomized equally to the intervention group receiving inhaled lipid nanoparticle-encapsulated anti-tubercular therapy with reduced oral components or the control group receiving standard oral combination therapy. Two participants in the intervention group withdrew because of relocation, while three participants in the control group discontinued because of severe gastrointestinal intolerance. Baseline analyses therefore included all 80 randomized participants, whereas complete-case six-week outcome analyses included 75 participants: 38 in the intervention group and 37 in the control group.

Table 1. Baseline Demographic and Clinical Characteristics of the Randomized Participants

Characteristic	Total Sample (N=80)	Intervention Group (n=40)	Control Group (n=40)	p Value
Age, years	38.4 ± 11.2	37.9 ± 10.8	38.9 ± 11.7	0.693
Sex, male/female, n	48/32	25/15	23/17	0.648
Body mass index, kg/m²	20.1 ± 2.8	20.3 ± 2.6	19.9 ± 3.0	0.528
Sputum smear grade, 3+/2+, n	52/28	27/13	25/15	0.639
Serum ALT, U/L	28.4 ± 6.5	28.1 ± 6.2	28.7 ± 6.9	0.686
Serum AST, U/L	26.2 ± 5.8	25.9 ± 5.5	26.5 ± 6.2	0.647
Serum creatinine, mg/dL	0.88 ± 0.14	0.87 ± 0.13	0.89 ± 0.15	0.531
Total SGRQ score	58.6 ± 9.4	58.2 ± 9.1	59.0 ± 9.8	0.706

Data are shown as or minus standard deviation unless something else is mentioned. ALT stands for alanine aminotransferase; AST stands for aspartate aminotransferase; SGRQ stands for St. George's Respiratory Questionnaire.

The groups that were randomly assigned were similar at the start. No important differences were found in age how many men and women there were, body mass index, sputum smear grade, liver or kidney test results or quality of life related to breathing. The average age of all the people in the study was 38.4 plus or minus 11.2 years and 48 people were men.

At week six the average time it took for sputum culture to change was 22.4 plus or minus 4.1 days for the group that got the treatment and 34.8 plus or minus 5.6 days for the group that did not get the treatment. The treatment led to a drop of 12.4 days in the time it took for the culture to change. This was a difference between the two groups. Sputum change by week six happened for 35 out of 38 people in the treatment group and 26 out of 37 people, in the control group. This meant that the rate of change was 21.8 percentage points higher and the chance of changing was 1.31 times higher compared to the control group.

Table 2. Comparison of Primary Bacteriological Outcomes at Week Six

Outcome	Intervention Group (n=38)	Control Group (n=37)	Effect Estimate (95% CI)	p Value
Time to sputum culture conversion, days	22.4 ± 4.1	34.8 ± 5.6	−12.4 (−14.7 to −10.1); Hedges g: −2.51	<0.001
Sputum conversion by week six, n (%)	35 (92.1)	26 (70.3)	21.8% (4.8% to 38.9%); risk ratio: 1.31 (1.04 to 1.65)	0.018

CI, confidence interval. Negative mean differences suggest the intervention group did better in terms of time to conversion. Confidence intervals and standardized effects were calculated using the group means, standard deviations, event counts and denominators that were reported.

Both groups had significant improvements in total SGRQ scores during the six-week intervention. However the intervention group had a drop in mean scores compared to the control group. The difference between the groups in terms of change was −12.6 points, which shows a standardized effect in favor of the intervention.

Serum ALT went up by 3.1 ± 4.2 U/L in the intervention group and by 25.9 ± 10.1 U/L in the control group. Analysis of repeated measures showed effects of time and treatment group, as well as a significant time-by-group interaction. This means the way hepatic enzymes changed was different between the groups.

At week six the average levels of ALT and AST were much lower in the intervention group than in the control group. Serum creatinine was not different between the groups. Gastrointestinal side effects happened in two people in the intervention group and in 11 people in the control group. The chance of having side effects was 24.5 percentage points lower, in the intervention group, which means a relative risk of 0.18.

Table 3. Changes in Respiratory Quality of Life and Serum ALT

Outcome	Group	Baseline	Week Six	Within Group Change	Between-Group Difference in Change (95% CI)	p Value
Total SGRQ score	Intervention (n=38)	58.2 ± 9.1	25.8 ± 6.3	−32.4 ± 7.2	−12.6 (−15.8 to −9.4); Hedges g: −1.78	<0.001
	Control (n=37)	59.0 ± 9.8	39.2 ± 7.5	−19.8 ± 6.8		
Serum ALT, U/L	Intervention (n=38)	28.1 ± 6.2	31.2 ± 5.8	3.1 ± 4.2	−22.8 (−26.4 to −19.2); Hedges g: −2.93	<0.001
	Control (n=37)	28.7 ± 6.9	54.6 ± 12.3	25.9 ± 10.1		

ALT, alanine aminotransferase; CI, confidence interval; SGRQ, St. George's Respiratory Questionnaire. The p value for ALT represents the reported time-by-group interaction. Negative differences in SGRQ change favour the intervention group; negative differences in ALT change indicate a smaller enzyme increase in the intervention group.

Table 4. Secondary Safety Outcomes at Week Six

Outcome	Intervention Group (n=38)	Control Group (n=37)	Effect Estimate (95% CI)	p Value
Serum ALT, U/L	31.2 ± 5.8	54.6 ± 12.3	−23.4 (−27.9 to −18.9); Hedges g: −2.42	<0.001
Serum AST, U/L	28.5 ± 5.1	*48.2 ± 10.6*	*−19.7 (−23.6 to −15.8); Hedges g: −2.35*	<0.001
Serum creatinine, mg/dL	0.85 ± 0.11	0.88 ± 0.13	−0.03 (−0.09 to 0.03); Hedges g: −0.25	0.284
Gastrointestinal adverse events, n (%)	2 (5.3)	11 (29.7)	−24.5% (−40.8% to −8.1%); risk ratio: 0.18 (0.04 to 0.74)	0.006

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval. Negative mean differences indicate lower week-six biochemical values in the intervention group.

DISCUSSION

This study looked at people who got a treatment. The treatment had medicine in a form that they inhaled. The medicine was isoniazid and rifampicin. They also took less of the pills for pyrazinamide and ethambutol (11,12). These people had results in their tests. Their sputum tests turned negative faster. They had a result at six weeks than people who took the usual pills. The group that inhaled the medicine also had damage to their liver. They had stomach problems. Their breathing and overall quality of life improved more. These results suggest that giving medicine directly to the lungs might work better. It might help get rid of the bacteria. It might also reduce the amount of medicine in the rest of the body during the part of treatment (13,14). The faster time for the test results to turn matches what experts thought would happen. Giving medicine through the lungs might keep the medicine in the lungs longer. It might protect the medicine from breaking down soon. It might also help the medicine get into the cells in the lungs. Some earlier studies have shown that inhaled medicines can help keep the amount of medicine in the lungs. They can also keep the medicine working in the lungs for longer. Getting

medicine to the cells is important because the bacteria can hide inside the bodys cells. Those cells are hard to reach with medicine.. The results from this study only show what happened in the first six weeks. They do not show that the treatment is complete. They do not prove that the treatment works term. They do not show that the bacteria stay away for good. They also do not show that the bacteria become resistant, to the medicine (15).

The liver test results show that people who got the inhaled lipid nanoparticle treatment had a smaller increase in serum ALT and AST. This is important because liver damage is a problem with the usual tuberculosis treatments and can mean that people have to stop treatment for a while or start taking the drugs one at a time again or change their treatment plan (16). The people who got the treatment had smaller increases in liver enzymes, which makes sense because they were not exposed to as much isoniazid and rifampicin in their whole body. However the people who got the treatment still had a big increase in ALT, which is a liver enzyme. So the results show that the inhaled treatment reduces liver damage. It does not completely prevent it.

The people who got the treatment also had fewer stomach problems. This is a thing because stomach problems can make it hard for people to keep taking their drugs especially when they have to take a lot of them for a long time. If people do not have to take many drugs by mouth that can be very helpful.. The inhaled treatment has its own set of problems like whether it is safe for the lungs, where the particles go in the body whether the carrier is safe how to keep the machine clean and whether people get the same dose each time (18,19). So just because the inhaled treatment causes stomach problems that is not enough to say it is better overall without also checking to make sure it is safe, for the lungs and doing more follow-up over time.

The big drop in SGRQ scores shows that people in the intervention group had an improvement in their breathing health in the short term. This could be because the bacteria in their lungs went down faster their breathing symptoms got better they had bad side effects or all of these things happened. We do not know for sure why people in this group had a quality of life because the study did not give us detailed information about their symptoms or how the treatment worked. So we should just say that the treatment was associated with an improvement in SGRQ scores after six weeks rather than saying that the treatment directly caused this improvement.

The study was done well in some ways. For example people were randomly assigned to groups and the people doing the study did not know who was in which group. The results were also measured without knowing who was in which group. The study also checked to make sure people were taking their medicine. It looked at the bacteria in their bodies the chemicals in their blood any bad side effects and what the patients themselves reported. The people in the study were similar at the start so it is unlikely that the results were due to differences between the groups at the beginning. The study also measured how quickly the bacteria, in peoples bodies went away and how many people had no bacteria after six weeks, which gives us an idea of how well the treatment worked.

There are some limitations that we need to think about when we look at this study. This study was done at one place. It did not have a lot of people in it which means the results may not be totally accurate and may not apply to everyone. The study looked at the people who finished the follow-up which was 75 people of looking at all 80 people who started the study. The treatment only lasted for six weeks so we do not know what happened to the people in the term like if they got sick again or had bad side effects.

We also need to remember that some people were not part of this study, like people who have serious health problems or people who have tuberculosis that is hard to treat.

It is also hard to repeat this study because we do not have all the details about how the treatment was made and given to the people. We do not know things like how much of each drug was used what the

drugs were mixed with and how well the treatment worked when it was given to the people. These are things to know because they can affect how well the treatment works and if it is safe (19,20).

Larger studies that involve centers should compare the treatment with the standard therapy that follows the guidelines throughout the entire time a person is being treated. These studies should use intention-to-treat analyses. More time is needed to look at relapse having a culture for a long time resistance, harm to organs, lung function how well people stick to their treatment and outcomes that matter to patients. Creating dry-powder versions of the treatment could help reduce the need for electrically powered machines that make a mist and could make storing and giving the treatment easier. However the way the powder moves, in the air how evenly it is. How well it reaches the lungs would need careful checking before it is used more widely in hospitals (17,20).

CONCLUSION

In adults who have just been diagnosed with sputum- pulmonary tuberculosis inhaled treatment that uses lipid nanoparticles to deliver anti-tubercular drugs was linked to faster culture conversion. This treatment also led to a rate of sputum conversion at six weeks. The treatment caused increases in liver enzymes. It also led to stomach and intestinal side effects. Patients also had improvement in their respiratory health and overall quality of life compared to standard oral therapy. These results suggest that targeted delivery of drugs to the lungs is worth study. However the study did not show long-term effectiveness. It also did not prove that the treatment prevents relapse. The study also did not show the safety of the treatment, beyond six weeks.

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21. Structured Abstract